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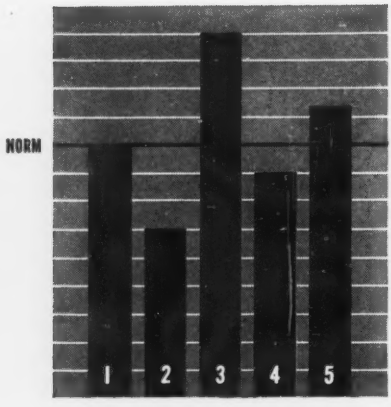

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HYPERCALCEMIC SYNDROME ASSOCIATED WITH ANDROGENIC AND ESTROGENIC THERAPY

JULIAN B. HERRMANN, M.D., EUGENE KIRSTEN, M.D. AND JOSEPH S. KRAKAUER, M.D.

*From the Montefiore Hospital, New York City**

IN RECENT years androgenic and estrogenic compounds have been employed in the treatment of breast carcinoma (1–7). Previous work has suggested that these hormones may occasionally cause hypercalcemia in patients with osteolytic metastatic mammary carcinoma (6, 8). Spontaneous hypercalcemia occurs not infrequently in debilitated patients suffering from osteolytic lesions secondary to mammary carcinoma. We have encountered six such instances in the past year and in some of these patients there have been recurrent episodes of hypercalcemia associated with nausea and vomiting.[1] Since hypercalcemia is the only serious complication reported to date apparently attributable to sex hormone therapy it appeared to be important to establish, if possible, the relationship of these hormones to the production of hypercalcemia.

The case histories are reported of four patients, three of whom developed hypercalcemia coincident with the administration of testosterone propionate and one with the administration of diethylstilbestrol. Three patients had mammary carcinoma and one patient had a reticulum-cell sarcoma. They were in the terminal stage of the disease and received hormonal therapy after all other therapeutic measures had been employed.

Case 1. (38687R) E.W., a 38-year-old white woman underwent a right radical mastec-

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* Division of Neoplastic Diseases, Dr. Daniel Laszlo's Service.

[1] Report to be published.

tomy about five and one-half years prior to her admission to the Montefiore Hospital in February 1947. Three years after the mastectomy she developed pleural, pulmonary, osseous and pelvic metastases for which she was surgically castrated. Subsequent to the castration she received high voltage irradiation to the metastatic areas. Some palliation was obtained from these therapeutic procedures. Later the patient's condition

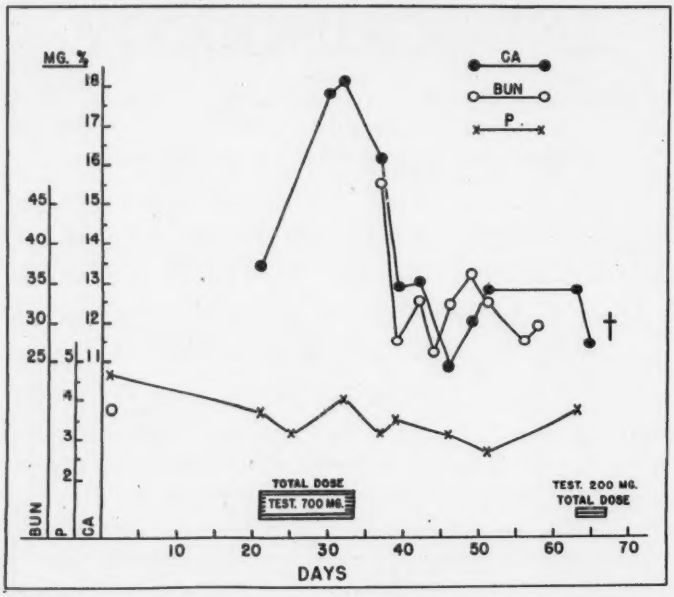

FIG. 1. Testosterone propionate administered to a patient with hypercalcemia caused a rapid elevation of the serum calcium. After termination of the initial period of testosterone therapy the serum calcium and blood urea nitrogen levels fell but did not return to normal levels. One month later a small amount of the hormone was administered for a period of four days. The patient died subsequently (time of death indicated by dagger).

deteriorated and she was admitted to the hospital because of generalized weakness and pain in the right hip.

Physical examination on admission to the hospital revealed numerous nodules in the skin of the right chest wall in the region of the mastectomy scar that were interpreted as metastatic mammary carcinoma. Roentgenologic studies disclosed evidence of widespread osteolytic and pulmonary metastasis. Aspiration of the sternum revealed almost complete replacement of the marrow by neoplastic cells. The blood urea nitrogen (BUN) and serum phosphorus were within normal limits.

Testosterone therapy was initiated three weeks after admission. The patient received 700 mg. of testosterone propionate over a period of twelve days. The serum calcium, which was somewhat elevated (13.5 mg. per cent) at the beginning of the treatment rose

to 18.1 mg. per cent on the eleventh day. The BUN was 47.3 mg. per cent five days later (Fig. 1). The urea clearance at this time was 33 per cent of normal.

Nausea and vomiting developed several days after the androgen therapy was initiated. The vomiting increased in severity and the patient later became lethargic. Her condition improved after the therapy was discontinued and large amounts of glucose, saline and 2.5 per cent sodium citrate, the latter in 250 cc. quantities, were administered parenterally. Concomitant with this improvement there was a decrease in the serum calcium and BUN values. The urinary output, which at the height of toxicity was 200 to 300 cc. daily, increased to over 2000 cc. daily. During the month subsequent to the withdrawal of testosterone the serum calcium and BUN remained moderately elevated and the urea clearance low. There were no toxic symptoms. The possibility existed that the hypercalcemia and azotemia were spontaneous and that their association with the administration of testosterone was coincidental.

About one month after termination of the first course of androgen therapy, testosterone propionate was again administered to the patient because of intractable pain. She received 50 mg. a day for four days. Therapy was terminated because she developed nausea and vomiting. The patient later became lethargic. Vigorous intravenous therapy was instituted but she became comatose and died four days after withdrawal of the testosterone. The serum calcium did not rise during the second and fatal toxic episode.

Postmortem examination revealed a recurrence of anaplastic mammary adenocarcinoma in the operative scar with metastasis to the left breast, lungs, thyroid, adrenals, left ureter, intestinal serosa, vertebrae, right innominate bone, sternum and ribs. Tumor obstruction of the left ureter had caused a hydronephrosis with compensatory hypertrophy of the right kidney.

Histopathologic examination of the right kidney disclosed narrowing of the lumina of the convoluted tubules with marked swelling and vacuolization of the tubular epithelium. Many calcium deposits were present in the renal tubules. There was metastatic calcification in the left lung and gastric mucosa. The left kidney was hydronephrotic. The parathyroids were normal grossly and microscopically.

Case 2. (MH42786) J.Y., a 48-year-old white woman had undergone a left radical mastectomy for carcinoma followed by roentgen castration two and one-half years prior to her admission to the Montefiore Hospital in April 1947. Her chief complaint on admission was generalized skeletal pain which had necessitated complete bed rest for a number of weeks. Physical examination revealed no evidence of recurrent disease but roentgenologic studies disclosed evidence of extensive osteolytic metastases.

The patient had received 900 mg. of testosterone propionate during the six days prior to admission and 300 mg. was administered during the first three hospital days. A serum calcium determination at this time was 13.6 mg. per cent; therefore testosterone therapy was stopped. Two days later the serum calcium was 14.6 mg. per cent and then it slowly returned to normal limits (Fig. 2). At no time was there any nausea, vomiting or lethargy.

Testosterone therapy was again instituted ten days after the serum calcium level had returned to normal limits, the patient receiving 50 mg. of the hormone every other day over a period of three weeks for a total dose of 650 mg. There was a gradual rise in the serum calcium from 9.6 mg. per cent to a peak of 16.1 mg. per cent reached six days after the therapy was terminated. There was a concomitant rise in the BUN. The urea clearance at this time was 22 per cent of normal. The hormone was withdrawn because the patient developed nausea, vomiting and lethargy. Glucose in saline and sodium

citrate solutions were administered parenterally and there was a gradual return to normal levels of the serum calcium and BUN and a concomitant cessation of the nausea and vomiting.

After a period of three weeks during which several determinations of the serum calcium and BUN revealed normal levels, testosterone therapy was once again instituted for intractable pain, the patient receiving 350 mg. of the hormone during a twelve-day period. The serum calcium quickly rose from a level of 9.1 mg. per cent to a peak of 17.2 mg. per cent three days after the withdrawal of the hormone. There was a concomitant rise in the BUN. Nausea and vomiting developed in association with the hypercalcemia.

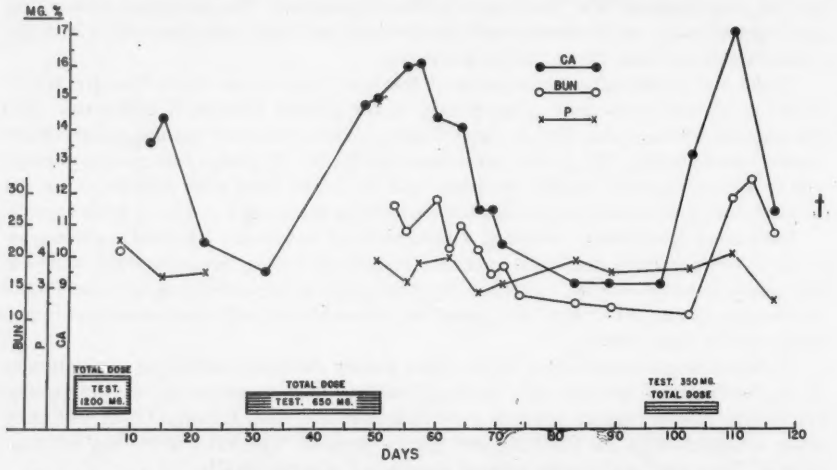

FIG. 2. Each succeeding episode of hypercalcemia was more intense, appeared more promptly and was produced by a smaller dose of testosterone propionate. Despite the fall in serum calcium and blood urea nitrogen levels associated with corrective therapy the patient died in uremic coma seventeen days after withdrawal of the testosterone propionate (time of death indicated by dagger).

Despite withdrawal of the hormone and the institution of vigorous parenteral glucose and saline therapy which was followed by a drop in the serum calcium and BUN, the vomiting persisted, the patient became lethargic, developed oliguria and died in uremic coma seventeen days after termination of the hormonal therapy. There was a terminal hyperpyrexia of 108° F.

Postmortem examination, limited to an abdominal incision, revealed metastatic mammary carcinoma in the lungs, pleura, tracheobronchial lymph nodes, liver and bones. The parathyroids were not obtained for examination.

Histopathologic examination of the kidneys revealed small areas of subcapsular fibrosis with round cell infiltration and an occasional hyalinized and fibrosed glomerulus. The glomeruli for the most part were normal. The tubules revealed degeneration of the lining epithelium and contained hyaline and granular casts. Calcium deposits were present, especially in the lumina of the collecting tubules, frequently involving the walls.

Case 3. (42419) M.R., a 40-year-old cachectic white woman had become aware of pain in both hips, fatigue and weight loss about one year prior to her admission to the Montefiore Hospital in April 1947. Five months subsequent to the onset of the pain in her hips she noted a painless mass in the left infraclavicular region and shortly thereafter similar masses in both supraclavicular areas. Biopsy of the infraclavicular mass revealed reticulum-cell sarcoma. Two months later intra-abdominal masses were discovered for

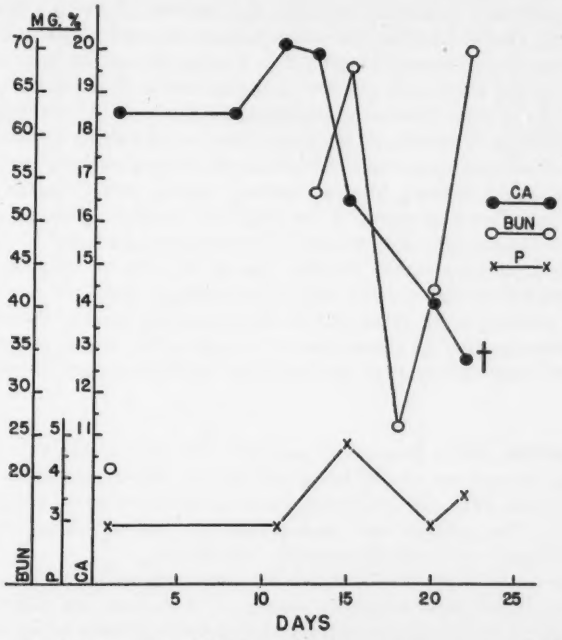

FIG. 3. The patient had received 1115 mg. of testosterone propionate for one month prior to admission to the hospital. No androgen therapy was administered after her admission. Following vigorous parenteral fluid administration there was a fall in the serum calcium and blood urea nitrogen levels. The low nitrogen level however was not sustained but rose until the patient's death (indicated by dagger).

which the patient received irradiation. Dyspnea and cough developed during this period.

The patient had been given 1115 mg. of testosterone propionate by her local physician during the month prior to her admission. Listlessness and nausea associated with frequent attacks of vomiting had been present during this month. No testosterone was administered during her hospital stay.

Physical examination on admission disclosed a nontender cervical, supraclavicular and inguinal adenopathy, bilateral pleural effusion, hepatosplenomegaly and nontender masses in the abdomen and pelvis. Roentgenologic studies revealed a moderate demineralization of all the vertebrae with collapse and anterior gibbus formation of the

eighth dorsal and erosion of the body of the fourth lumbar vertebrae. The patient was semiambulatory.

The serum calcium on admission was 18.5 mg. per cent, the BUN 21.4 mg. per cent and the phosphorus 2.8 mg. per cent (Fig. 3). The serum calcium rose to a maximum level of 20.1 mg. per cent on the eleventh hospital day and the BUN reached a peak of 68.8 mg. per cent on the fifteenth day at which time the serum phosphorus was 4.8 mg. per cent and the urea clearance 18 per cent of normal. Concomitant with these changes there were persistent vomiting, lethargy and oliguria. Following intensive therapy with parenteral glucose in saline the serum calcium fell gradually to a level of 12.6 mg. per cent on her twenty-second hospital day. During this period there was also a temporary drop in the blood urea nitrogen and phosphorus, a moderate improvement in urinary output and some decrease in the toxic symptoms. Renal insufficiency with a rise in BUN supervened, however, and the patient died on her twenty-third hospital day.

Postmortem examination revealed reticulum-cell sarcoma of the spleen, liver, pancreas, right adrenal gland, urinary bladder, ureters, uterus, cervix, vagina and vertebrae. There was congestion and edema of the lungs and marked dilatation of the stomach. The parathyroids grossly and microscopically were not remarkable.

Histopathologic examination revealed the kidneys to be congested, the capsules irregularly thickened and covered with a hemorrhagic fibrinous exudate. There was pronounced swelling of the renal tubules with numerous areas of vacuolar and hyaline droplet degeneration but no glomerular damage. Many of the larger collecting tubules contained red blood cells and the tubules of the cortex and medulla contained calcium deposits.

Case 4. (42708) D.S., a 58-year-old cachectic white woman had undergone a modified right radical mastectomy about five years prior to her admission to the Montefiore Hospital in March 1947. Her chief complaints on admission were pain in the lower back and dyspnea. The patient was semiambulatory. Roentgenologic studies disclosed massive pulmonary and multiple osteolytic metastases.

Estrogenic hormone in some instances has caused regression of pulmonary metastases secondary to breast cancer in elderly women (1, 2, 3, 4, 5). On this basis, diethylstilbestrol therapy, 2 mg. administered intramuscularly three times a day, was instituted on May 5, 1947. Several days later the dose was increased to 5 mg. three times a day until a total of 78 mg. had been administered over a period of fourteen days. Shortly after therapy was instituted the patient began to complain of anorexia and weakness. This was interpreted as an immediate reaction which occurs frequently in the diverse conditions for which diethylstilbestrol is employed. However, when listlessness and depression developed the estrogen therapy was terminated. Intensive treatment with parenteral fluids produced a gradual symptomatic improvement.

The chemical changes in the blood coincident with the toxic manifestations are shown in Fig. 4. Unfortunately the pretreatment chemical studies are incomplete. A hypercalcemia of 16.4 mg. per cent was found two days after institution of estrogen therapy. A peak of 19.9 mg. per cent was reached five days later and then the level fell precipitously during the remainder of the period of administration of diethylstilbestrol. The serum BUN and phosphorus followed a similar pattern. A urea clearance determination during this period was 25 per cent of normal. Clinical improvement became noticeable after withdrawal of the drug and institution of parenteral fluid therapy. Subsequently the patient's general condition remained satisfactory and the serum calcium, phosphorus and BUN remained within normal limits.

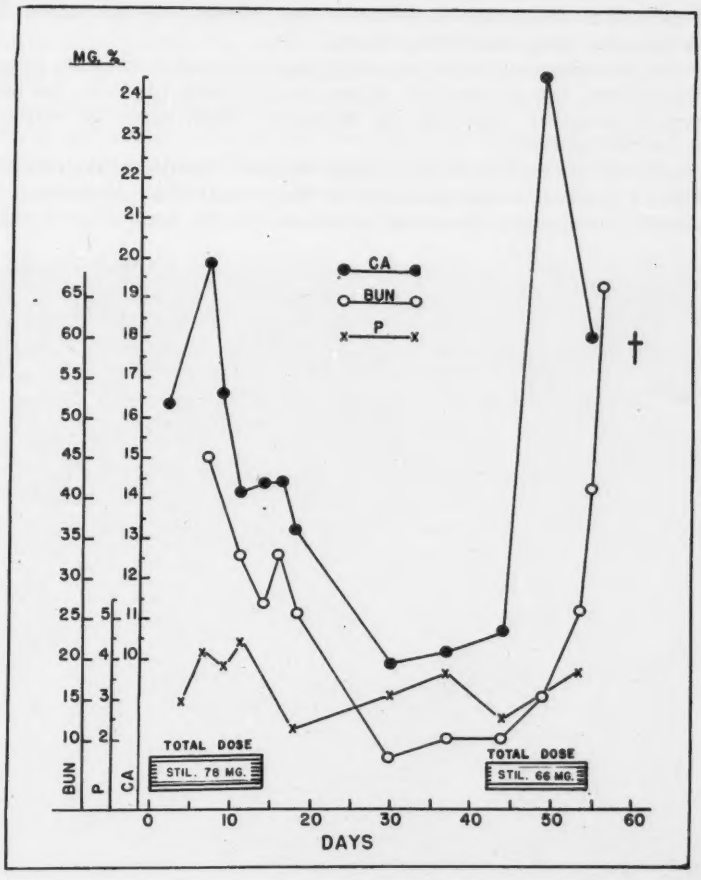

FIG. 4. There was an elevation of the serum calcium and blood urea nitrogen levels associated with diethylstilbestrol administration. After reaching a peak these levels fell during the continued administration of the estrogen. A subsequent episode with greatly elevated calcium and blood urea nitrogen levels was produced by a smaller amount of the estrogen and resulted fatally (indicated by dagger). The calcium level, as in the first episode, fell during the course of the estrogen therapy.

After the levels of calcium, phosphorus and BUN in the patient's serum had been within normal limits for several weeks diethylstilbestrol therapy was again instituted because of persistent pain and dyspnea. A total of 66 mg. was administered over a period of twelve days. The urea clearance was 29 per cent of normal prior to the second course of stilbestrol therapy. The serum calcium rose from 10.2 mg. per cent to a peak of 24.5 mg. per cent within seven days and then decreased during the continued administration of the estrogen. The clinical toxic manifestations were similar to those previously described.

Vigorous parenteral glucose and saline therapy was instituted but the patient died in coma five days after withdrawal of the estrogen.

Postmortem examination revealed anaplastic mammary adenocarcinoma metastatic to the lungs, pleura, thyroid, pituitary, thymic area, sternum, ribs, liver, left adrenal, periesophageal, perigastric, periaortic and mesenteric lymph nodes, the dorsolumbar vertebrae and the right ilium.

Histopathologic examination of the kidneys revealed dilatation of the tubules with vacuolization and granular degeneration of the tubular epithelium. Numerous areas of calcific deposits were found in the tubular epithelium (Fig. 5). Nests of tumor cells were

FIG. 5. The deeply stained areas are calcium deposits in the renal tubules.

seen in the peripelvic lymphatics. The thyroid contained many foci of tumor cells and numerous deposits of calcium were scattered throughout the gland. The parathyroid glands were moderately hyperplastic and composed of small chief cells and occasional oxyphilic cells.

DISCUSSION

Steroid hormones apparently exert a profound influence on calcium metabolism. Irradiated ergosterol mobilizes calcium and may produce hypercalcemia in dogs and in man (9, 10). Estrogens and androgens may decrease the urinary and fecal excretion of calcium and convert a negative into a

positive calcium balance in patients with osteoporosis (11). Androgenic hormones may produce in some women roentgenologic evidence of calcification in areas of osteolysis secondary to breast carcinoma (6, 7).

Occasionally toxemia, associated with hypercalcemia and a subsequent azotemia, follows the administration of androgens and estrogens to women with osteolytic lesions. Four examples of this phenomenon are reported here. In three patients there were osteolytic lesions secondary to mammary cancer and in the fourth the osteolytic lesions were associated with reticulum-cell sarcoma. It would appear that the property possessed by these hormones to produce hypercalcemia is not specific for cases of osteolytic mammary cancer. The production of hypercalcemia in patients with osteolytic mammary carcinoma following the administration of natural estrogens has been reported (8); but this is the first time to our knowledge that this phenomenon has been produced by a synthetic estrogen.

The hypercalcemia induced by the sex hormones caused nausea, vomiting and dehydration which precipitated the renal toxemia. The excretion through the kidneys of calcium mobilized by the sex hormones produced a calcinosis of the renal tubules with progressive renal impairment. Ultimately the kidneys were so badly damaged that the excretion of calcium and nitrogenous waste products was greatly diminished with resultant renal insufficiency. A similar phenomenon has been described in connection with the administration of parathyroid hormone (12) and with ergosterol therapy (9, 13, 14). It is quite possible that the degree of renal impairment present before the institution of hormonal therapy was a factor in determining the rapidity of onset of this toxic phenomenon.

It is significant that the patient (Case 1) who succumbed to a relatively small amount of testosterone was found at autopsy to have one hydronephrotic kidney and calcinosis of the opposite one. Reinstitution of hormonal therapy with smaller amounts of the sex hormones in Cases 1, 2 and 4 produced a more prompt and severe toxic reaction than was encountered in the first episode. In Case 1 the second course of testosterone proved fatal without producing an elevation of the serum calcium. The increase in toxicity of the hormones noted in successive periods of hormonal therapy was apparently the result of cumulative renal damage.

In addition to pre-existent renal damage a contributory factor in the production of the hypercalcemia may be immobilization. Hypercalcemia, calcinuria and renal lithiasis may occur in individuals who are immobilized even for relatively short periods of time (15). Mobilization of calcium with the production of osteoporosis is also associated with cachexia. The patients described here who developed hypercalcemia after sex hormone therapy exhibited varying degrees of cachexia and were either bedridden

or semiambulatory. We have not encountered sex hormone-induced hypercalcemia in ambulatory patients.

It may be possible to realize the therapeutic possibilities of the sex hormones in the treatment of cancer and to reduce the incidence of hypercalcemic toxemia as a complication of this therapy by the judicious selection of patients. Patients with pretreatment hypercalcemia preferably should not receive sex hormone therapy. Those who are bedridden or whose renal function is markedly impaired should be treated cautiously. Frequent blood chemical and kidney function studies should be performed. Adequate fluid intake should be maintained at all times. Listlessness, nausea, vomiting and an increase in serum calcium or evidence of progressive renal impairment should be a warning to abandon sex hormone therapy.

In addition to the discontinuation of hormonal therapy there is one measure which may be employed for the purpose of reducing the amount of ionized calcium (Ca^{++}) in the blood and tiding the patients over the critical period. This consists in the administration of sodium citrate in a 2.5 per cent solution in amounts of 250 cc. at four-hour intervals until symptomatic improvement is apparent (16). This measure achieves its effect by converting the relatively insoluble Ca^{++} ions into soluble, weakly ionized calcium citrate ions. This conversion will not alter the total serum calcium values as determined by the conventional analytical methods but will alter the ratio between the Ca^{++} and (Ca citrate^{-}) ions. Its administration should be discontinued once the serum calcium values have fallen to the normal levels. Overdosage with sodium citrate can be avoided by watching for the development of a Chvostek reaction, indicative of impending tetany.

The intravenous infusion of glucose, saline and of sodium citrate after withdrawal of the androgen was followed in Cases 1, 2 and 3 by the return to lower values of the serum calcium and BUN and alleviation of toxic symptoms. In the case of the patient receiving diethylstilbestrol the serum calcium level fell and continued to fall during the period of estrogen administration although it did not return to normal levels during this period. Clinical improvement of the toxic manifestations became evident only after the withdrawal of the estrogen and the institution of parenteral fluid therapy.

SUMMARY AND CONCLUSIONS

1. In the course of therapy with testosterone propionate and diethylstilbestrol, four patients, three with osteolytic lesions secondary to mammary carcinoma and one with an osteolytic lesion of a reticulum-cell sarcoma, developed toxic reactions, associated with hypercalcemia and signs and symptoms of renal insufficiency.

2. Several of these toxic episodes were corrected by the cessation of hormonal therapy and the institution of parenteral therapy consisting of infusions of saline, glucose and sodium citrate. Subsequent toxic episodes following reinstitution of hormonal therapy proved irreversible and had a lethal outcome.

3. All the patients sustained renal damage with nephrocalcinosis.

4. The rationale is presented for the therapeutic use of sodium citrate (2.5 per cent) infusions for hypercalcemic states such as encountered in this study.

5. The hypercalcemic syndrome appears to occur relatively infrequently in patients with osteolytic lesions treated with these hormonal agents. Its incidence might be reduced by careful screening of the patients selected for hormonal therapy. Several criteria for the selection of appropriate cases are suggested.

Acknowledgments

The authors are indebted to Dr. H. M. Zimmerman and staff for the pathologic studies and to Dr. Ephraim Shorr for his suggestions and advice during this investigation. The testosterone propionate (Oreton) was kindly supplied by Dr. Edward Henderson of the Schering Corporation, Bloomfield, New Jersey.

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RENAL EXCRETION AND TUBULAR REABSORPTION OF SALT IN CUSHING'S SYNDROME AFTER INTRAVENOUS ADMINISTRATION OF HYPERTONIC SODIUM CHLORIDE*

JOSEPH P. KRISS, M.D.,† AND PALMER H. FUTCHER, M.D.‡

From the Department of Internal Medicine, Washington University School of Medicine, Saint Louis, Missouri

OF THE two mechanisms by which the kidneys regulate the excretion of salt,[1] glomerular filtration and tubular reabsorption, changes in the former have been shown to be of importance in the pathogenesis of edema observed in certain patients with congestive heart failure. In such patients, Merrill (1) has shown that markedly reduced glomerular filtration contributes to the abnormal retention of injected sodium chloride observed by Futcher and Schroeder (2). Despite the fact that the rate of glomerular filtration is frequently reduced also in patients with Addison's disease (3), such patients lose salt in the urine to an abnormally great degree. On the basis of this and other evidence, it seems likely that deficiency of adrenal hormones results in a diminished capacity of the renal tubular cells to reabsorb salt. The reverse effect (increased capacity) has not been demonstrated to occur in that form of adrenal *hyper*function which results in Cushing's syndrome. Indeed, Soffer *et al.* (4) have observed that when desoxycorticosterone acetate (DCA) and salt are administered to patients with Cushing's syndrome, these subjects excrete salt to a *greater* degree than do normal subjects similarly treated.

This investigation was undertaken in order to study tubular reabsorption of salt in patients with Cushing's syndrome. Observations have been made on the influence of an intravenous injection of a large amount of sodium chloride upon the rate of salt excretion, the renal filtration rate and plasma flow in these subjects.

METHODS

All experiments were conducted according to the following standard routine: The subjects ingested no food or fluid during the 3-hour period of

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† Present address: 536 Mason Street, San Francisco, California.

‡ Present address: Johns Hopkins Hospital, Baltimore, Md.

[1] In the exposition which follows, we have used the term "salt" synonymously with the term "sodium chloride."

observation and no food after 6 p.m., the night before. All subjects except J. K. (control) were hospitalized. All except J. K. and L. P. had ingested for at least three days a normal diet supplying approximately 3 to 5 Gm. of sodium chloride daily (calculated from content of sodium) and were allowed additional sodium chloride from a shaker as desired. J. K. ingested a normal, salted diet not prepared in the hospital. L. P. ingested for four days preceding the experiment a normal, measured diet supplying 10 Gm. of sodium chloride daily. On the morning of the test, the glomerular filtration rate and the renal plasma flow were determined during two successive control clearance periods of about 15 minutes each by measuring the mannitol and the para-aminohippurate (PAH) clearances, respectively. Solution of sodium chloride (0.85 per cent) injected intravenously at a rate of 4 cc. per minute was the vehicle for the mannitol and PAH infusion. Immediately after the second clearance period had been terminated, 400 cc. of 5 per cent sodium chloride in water was injected intravenously in about 50 minutes. This amount of salt was sufficient to cause an average temporary increase in the plasma chloride concentration of about 13 mEq. per liter. Mannitol and PAH concentrations in the hypertonic salt solution were adjusted so as to maintain constant plasma levels of these substances. Measurements of renal clearance were made during the two approximately 25-minute periods required for the infusion of 5 per cent sodium chloride. After the hypertonic salt solution had been administered, the clearance infusion mixture used for the two preliminary periods was re-instituted and observations made for two or more 15-minute clearance periods.

Urine was collected from a catheter inserted into the bladder. Twenty cc. of sterile water followed by 20 cc. air were used to wash the bladder at the end of each collection period. Blood samples were drawn from an antecubital vein approximately at the midpoints of the clearance periods; plasma levels of mannitol, PAH, and chloride at the midpoints were obtained by interpolation between observed values.

Mannitol was determined according to the method of Smith *et al.* (5). Cadmium sulfate was used to precipitate protein from plasma and urine, as recommended by Goldring and Chasis (6). Among factors which were considered in performing the mannitol, plasma and urine blanks were nonfermentable reducing substances contributed by the plasma and urine (Factor 1); reducing substances contributed by the yeast suspension[2] (Factor 2); and adsorption or destruction of mannitol by the yeast suspension (Factor 3). In performing the plasma and urine blanks in the second experiment on F. B., and in the experiment on L. P., all factors were

[2] Starch-free yeast was donated by Anheuser-Busch Company, Inc., Saint Louis, Missouri.

compensated for. No urine blank was employed in the other experiments, and only Factor 1 was compensated for in performing the plasma blank. Details of the method employed for calculation of the mannitol blanks will be presented in a separate report (7). PAH was measured as recommended by Smith *et al.* (8). The chloride content of plasma was determined as described by Van Slyke (9); that of urine was measured by the Volhard-Arnold technique (10). Urine and plasma sodium concentrations were measured by the technique of Butler and Tuthill (11). Values for clearance rates were calculated according to the method of Möller *et al.* (12). All values for clearance rates and excretion rates for chloride and water were corrected to a standard body surface area of 1.73 square meters, calculated from the DuBois height-weight formula (13).

SUBJECTS

The experimental subjects included 3 patients with Cushing's syndrome and 3 other subjects who served as controls. None of the control subjects manifested arterial hypertension or clinical evidence of renal disease. Two patients with Cushing's syndrome (G. S. and F. B.) had hypertension. Case summaries relating to the patients with Cushing's syndrome are presented below.

G. S., Cushing's syndrome (Barnes Hosp. 143750): This 35-year-old white woman was admitted February 6, 1947, because of abdominal swelling, weight gain, reddening of the skin, hypertension, and glycosuria, developing over a 3-year period following a hysterectomy for bleeding. Examination revealed a moon-shaped face, obese neck and shoulders, thin extremities and skin, arteriolar narrowing in the optic fundi, normal visual fields, rales at both lung bases, an enlarged heart, distended abdomen, violet striae over the abdomen and breasts, and a blood pressure averaging 170/110. Blood counts were normal. Urinalysis revealed a specific gravity of 1.029, and a 3 plus reaction for sugar. The blood nonprotein nitrogen was 19 and the sugar (fasting) 205 mg. per cent. The serum albumin and globulin were 3.8 and 1.6 Gm. per cent respectively. The serum cholesterol was 385, phosphorus 3.8, and calcium 11.0 mg. per cent. A phenolsulfonphthalein renal test revealed 35 per cent excretion of the dye in 15 minutes. On February 17, 1947, the glomerular filtration rate, corrected to a surface area of 1.73 square meters, was 108 cc./min. and the renal plasma flow 313 cc./min.; the filtration fraction was 0.35. The basal metabolic rate was minus 2 per cent. Lumbar puncture revealed an initial pressure of 330 mm. of water with a final pressure of 260 mm., after removal of 10 cc. of fluid. The serum electrolyte pattern is presented at the top of the next page.

X-ray examination revealed demineralization of the clinoid process of the sella turcica, arteriosclerosis of the pelvic blood vessels, moderate cardiac enlargement, and several callus-like areas on the left tenth and right fifth, eighth, and eleventh ribs in the axillary region. Intravenous pyelograms revealed no abnormalities. The diabetes mellitus was moderately severe; 50 units of insulin daily was necessary to control glycosuria when the intake of carbohydrate was 180 Gm. A Hickey-Hare test for diabetes insipidus (14) performed by Dr. Alfred Kahn on February 21, 1947, was negative. On February 19,

Date	CO_2 combining power	Cl	Na	K[3]	Comment
	mEq./l.	mEq./l.	mEq./l.	mEq./l.	
2/ 8/47	38.2	95			
2/15/47	34.8	97	143.7		
2/21/47	25.8	100	143.5	4.96	
2/25/47					Exploratory laparotomy
3/ 2/47	35.7	84			
3/ 4/47	38.4	90			
3/ 5/47					KCl, 4–8 Gm. per day, initiated
3/ 6/47	35.0	95			
3/10/47	28.4	95			
3/15/47	26.6	102			KCl therapy stopped.
3/24/47					"Salt clearance" test.
3/25/47	31.7	98	145.1		

1947, the urinary excretion of 17-ketosteroids was 4 mg. per 24 hours and that of sodium pregnanediol glucuronidate was 11 mg. per 24 hours.[4]

Exploratory laparotomy was performed on February 25, 1947, by Dr. Peter Heinbecker. The subcutaneous tissues were thin, and the muscles were thin and friable. The ovaries were atrophic. Nothing abnormal was found in the pancreas, kidneys, or adrenals. The patient manifested an extremely stormy postoperative course complicated by atelectasis, laryngitis, and partial wound disruption. She gradually improved and regained her preoperative state. The abdominal wound remained defective, in that tissue layers beneath the skin failed to unite.

F. B., Cushing's syndrome (Barnes Hosp. 141970): This 20-year-old white housewife had been under observation since December, 1946, when she complained of gradual weight gain, decrease in the amount of hair on her scalp and increase in the amount of hair on her face, purple striae, headaches, and amenorrhea; the duration of these symptoms was one year. A physician had noted hypertension. Examination revealed an obese girl, with a rounded, florid face. The skin showed many purple striae over the buttocks, thighs, breasts, and axillae. There were fat-pads over the neck, shoulders and hips. A moderate increase in hair was noticeable over the face, the shoulders, arms and legs. Acne was present on the face and upper arms. Male distribution of hair was evident over the pubic region. There were no abnormalities of the external genitalia. The visual fields were normal. The blood pressure averaged 150/105. Blood counts were normal.

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[3] Measurement of potassium was performed in the laboratory of Dr. Alexis F. Hartmann.

[4] These measurements of steroidal excretion were made by Dr. Willard M. Allen. Ketosteroids were determined on the neutral steroid fraction obtained by hydrolysis of the butyl alcohol extract of urine, employing the metadinitrobenzene reagent. Glucuronidate was measured by the Allen-Viergiver method (15), which does not specifically identify the steroid as pregnanediol.

Urinalysis showed a few red cells and white cells per high power field in the sediment. Blood nonprotein nitrogen was normal as were the serum protein, calcium, phosphorus, cholesterol and phosphatase. A glucose tolerance test employing 1 Gm. of glucose per kilo, revealed the blood sugar (fasting) to be 80 mg. per cent; half-hour, 165 mg.; 1-hour, 215 mg.; 2-hour, 209 mg.; 3-hour, 105 mg.; and 4-hour, 39 mg. per cent. Additional chemical data follow:

Date	Serum CO_2 combining power	Serum chloride	Serum sodium	17-ketosteroid excretion in urine[4]	Sodium pregnanediol glucuronidate excretion[4] in urine
	mEq./l.	mEq./l.	mEq./l.	mg./24 hrs.	mg./24 hrs.
1/17/47	28.1	96	139.8	24	33
4/12/48	30.6	106	145.2	27	45

A phenolsulfonphthalein renal test revealed 40 per cent excretion of the dye in 15 minutes. The urine was concentrated to a specific gravity of 1.032. On January 15, 1947, the glomerular filtration rate was 102 cc./min., renal blood flow 452 cc./min., filtration fraction 0.23 and Tm_{PAH} 66.0 mg./min., corrected to a surface area of 1.73 square meters. Lumbar puncture revealed an initial spinal fluid pressure of 260 mm. of water and a final pressure of 240 mm. The basal metabolic rate averaged minus 20 per cent. Intravenous pyelograms were normal. On January 21, 1947, an exploratory laparotomy was performed by Dr. Peter Heinbecker. The ovaries were found to be atrophic, but no other abnormalities were found in the pelvis, adrenals, kidneys, or pancreas. The postoperative course was uneventful. On April 8, 1947, a Hickey-Hare test for diabetes insipidus (14) was negative. Six days later the first "salt clearance" test here reported on this patient was performed.

In April, 1948, aside from a slight weight gain, her condition was essentially unchanged. The basal metabolic rate was minus 27 per cent. A second "salt clearance" test was performed on April 7, 1948. A Soffer test (4) on April 12, 1948, showed that the patient excreted 37.2 per cent of injected salt before administration of desoxycorticosterone acetate (DCA) and 17.5 per cent after administration of DCA; these findings were interpreted as a normal response.

L. P., Cushing's syndrome: Psychoneurosis (Barnes Hosp. 159194): This 16-year-old unmarried white girl, admitted on May 19, 1948, stated that one year before she had noted the onset of amenorrhea, increased appetite with a rapid weight gain of 60 pounds, and an increase in hair over the face and body; subsequently she noted pains in her extremities, occasional frontal headache and the appearance of lineae striae. She had been treated with desiccated thyroid and with injections, probably containing estrogenic material, until six weeks preceding admission; concomitantly with this therapy she began to bleed irregularly from the vagina. A right mastoidectomy had been performed at age of 10 months. Two sisters were said to have considerable facial hair; there was no family history of marked obesity. Examination revealed an obese girl weighing 190 pounds. The wrists and fingers were delicate. There was moderate increase in the hair of the torso and the sideburn area of the face. There was acne of the face. There were

TABLE 1. EFFECT OF INTRAVENOUS INFUSION OF 5 PER CENT SODIUM CHLORIDE SOLUTION UPON RENAL FUNCTION OF CONTROL SUBJECTS AND OF PATIENTS WITH CUSHING'S SYNDROME

Subject	Period	Renal excretory rates*			Plasma			Mannitol† U/P	Mannitol U/P† / Chloride U/P	Comment
		Water	Sodium	Chloride	Chloride	Clearance*				
						Mannitol	PAH			
		cc. per min.	mEq. per min	mEq. per min.	mEq. per liter	cc. per min.	cc. per min.			
F.M. ♀ 15 yrs.	1	3.28	0.361	0.269	102.1	88.9	534	26.9	33.5	
Convalescent from meningitis.	2	3.57	0.400	0.320	104.7	104	680	28.5	34.5	
	3	3.59	0.514	0.363	100.8	106	546	28.7	31.1	5% NaCl
Ht. 63 in.; wt. 105 lbs.	4	4.27	0.691	0.526	112.6	110	796	25.7	23.5	5% NaCl
S.A.‡ 1.47 sq. m.	5	4.98	1.04	0.786	116.6	118	821	23.7	17.6	
Date 1/29/47	6	6.35	1.34	1.10	116.4	120	860	19.0	12.8	
R.G. ♂ 50 yrs.	1	2.77	0.271	0.189	98.0	115	686	41.8	60.4	
Undiagnosed back pain	2	4.05	0.313	0.245	98.6	119	788	29.2	47.6	
Ht. 66.5 in.; wt. 125 lbs.	3	2.92	0.314	0.239	102.5	108	675	37.2	46.6	5% NaCl
S.A. 1.65 sq. m.	4	3.24	0.461	0.370	107.7	125	823	44.9	43.5	5% NaCl
Date 2/3/47	5	3.21	0.491	0.409	109.2	113	770	36.5	31.3	
	6	2.75	0.445	0.398	110.0	107	632	39.1	29.8	
	7	4.08	0.606	0.616	108.1	132	821	32.6	23.4	
	8	3.31	0.524	0.530	105.5	113	648	34.1	22.7	
J.K. ♂ 28 yrs.	1	6.26	0.372	0.337	97.1		648			
Normal.	2	7.36	0.474	0.420	100.4	149	787	20.2	28.1	
Ht. 70.5 in.; wt. 178 lbs.	3	5.44	0.665	0.605	104.4	105	611	19.0	19.1	5% NaCl
S.A. 2.00 sq. m.	4	6.80		0.995	103.8	142	664	20.9	14.8	
Date 2/10/47	5	6.81	1.02	1.01	107.2	132	631	19.5	14.1	
	6	6.90	1.03	1.07	106.0		601			
G.S. ♀ 35 yrs.	1	4.32	0.365	0.281	98.6	114		26.3	40.0	
Cushing's syndrome.	2	4.40	0.331	0.327	99.3	118		26.9	35.9	
Ht. 59 in.; wt. 125 lbs.	3	8.10	1.17	0.908	106.6			15.4#	14.7#	5% NaCl
S.A. 1.52 sq. m.	4	13.9	2.45	2.18	117.0			10.1#	7.60#	5% NaCl
Date 3/24/47	5	13.0	2.45	2.18	117.0			10.3#	7.15#	
	6	8.91	1.66	1.47	114.0			13.3#	9.19#	
F.B. (1) ♀ 20 yrs.	1	3.24		0.319	102.2	127	553	39.6	41.8	
Cushing's syndrome.	2	3.15		0.287	102.4	134	600	42.6	47.5	
Ht. 64 in.; wt. 167 lbs.	3	5.45		0.748	106.4	147	910	27.1	21.0	5% NaCl
S.A. 1.82 sq. m.	4	11.0		2.01	112.3		806	17.8#	11.0#	5% NaCl
Date 4/14/47	5	10.1		2.00	112.5		700	20.8#	11.8#	
	6	7.55		1.57	114.9		761	24.1#	13.2#	
F.B. (2) ♀ 21 yrs.	1	2.39	0.268	0.160	102.2	81.5	446	34.1	51.8	
Cushing's syndrome.	2	2.74	0.318	0.190	102.1	91.0	501	33.3	49.0	
Ht. 64 in.; wt. 179 lbs.	3	3.49	0.500	0.362	105.1	89.0	496	25.5	25.8	5% NaCl
S.A. 1.88 sq. m.	4	7.30	1.41	1.25	111.2	104	575	14.3	9.23	5% NaCl
Date 4/7/48	5	7.81	1.62	1.47	112.4	105	535	13.4	7.98	
	6	6.32	1.28	1.20	111.9	115	535	18.2	10.7	
L.P. ♀ 16 yrs.	1	5.07	0.680	0.628	106.4	92.8	443	18.3	15.8	
Cushing's syndrome.	2	4.34	0.586	0.528	105.3	84.9	397	19.5	16.8	
Ht. 69 in.; wt. 188 lbs.	3	5.32	0.798	0.707	108.7	84.5	402	15.9	13.0	5% NaCl
S.A. 2.02 sq. m.	4	6.42	1.13	1.05	113.9	86.2	429	13.4	9.44	5% NaCl
Date 5/28/48	5	6.45	1.19	1.10	114.6	83.8	399	13.0	8.78	
	6	6.97	1.26	1.18	114.7	97.1	426	13.9	9.40	

* Corrected to a standard body surface area of 1.73 square meters.
† For explanation of these ratios, see text.
‡ S.A. signifies body surface area.
# Maximum values only, due to analytical difficulties; true figure is lower.

pinkish striae on breasts, arms and legs. The breasts were flat but about 10 cm. in diameter. The highest recorded blood pressure was 158/96 on admission; subsequent daily readings averaged 120/70. Dr. Willard M. Allen noted no abnormalities of the pelvic organs other than slight enlargement of the clitoris and a small erosion of the cervix which bled after manipulation; later, during her stay in the hospital, the patient bled slightly from the vagina. Blood counts were normal. The urine contained a trace of reducing substance in two of four random specimens. Plasma protein and serum calcium, phosphorus, and alkaline phosphatase concentrations were at normal levels. The plasma carbon dioxide combining power was 26.9 mEq./l.; the plasma chloride level was 103 mEq./l., and that of cholesterol 338 mg. per cent. Oral administration of 1 Gm. of glucose per kilo produced the following blood sugar curve: fasting, 105 mg. per cent; half-hour, 129 mg.; 1-hour, 208 mg.; 2-hour, 222 mg.; and 3-hour, 167 mg. per cent. Reducing substance appeared in the urine during the test. A glucose-insulin tolerance test conducted by Dr. W. Perry, involving the simultaneous oral administration of 1 Gm. of glucose per kilo and 0.1 unit of regular insulin per kilo intravenously, affected the blood sugar as follows: fasting, 77 mg. per cent; 20 minutes, 80 mg.; 30 minutes, 84 mg.; 60 minutes, 133 mg.; 90 minutes, 159 mg.; and 120 minutes, 167 mg. per cent. The basal metabolic rate averaged minus 3 per cent. Renal phenolsulfonphthalein excretion was 20 per cent in 15 minutes. After lumbar puncture, the initial pressure of the spinal fluid was 190 mm. of water. The 24-hour urinary excretion of 17-ketosteroids was 8.0 mg. and that of sodium pregnanediol glucuronidate 31.0 mg.[4] X-ray examination of the skull revealed hyperostosis frontalis interna; the sella was normal. Intravenous pyelograms revealed no indication of abnormalities of kidneys or adrenals. A psychiatric consultant found evidence of a mixed type of psychoneurosis.

As suggested by Dr. Willard M. Allen, this patient might well be classified not as an example of full-blown Cushing's syndrome, but as an example of "pseudo-Cushing's syndrome"—a term applied by Dr. Allen to patients manifesting obesity, amenorrhea, and hirsutism as the essential clinical abnormalities. However, this patient exhibited, in addition, the diminished tolerance to glucose administration characteristic of Cushing's syndrome and appeared resistant to the hypoglycemic action of insulin.

RESULTS

Chloride excretion—Chloride excretion rates in 3 experiments on 3 control subjects and in 4 experiments on 3 patients with Cushing's syndrome are presented in Table 1 and Figure 1. Prior to the injection of 5 per cent sodium chloride, chloride excretion rates were approximately the same for all subjects save L. P.; the latter patient manifested a higher rate of excretion. Following the start of the injection, 2 patients with Cushing's syndrome (G. S. and F. B.) exhibited a much more pronounced and prompt chloride diuresis than did the control subjects. Excretion of sodium paralleled that of chloride (Table 1).

Water excretion—Concomitant with the marked chloride excretion observed in 2 of the patients with Cushing's syndrome, there was observed increased urine flow (Table 1 and Figure 2). The urine flows in the control subjects and in 1 patient with Cushing's syndrome (L. P.) did not change markedly during the injection of hypertonic salt solution.

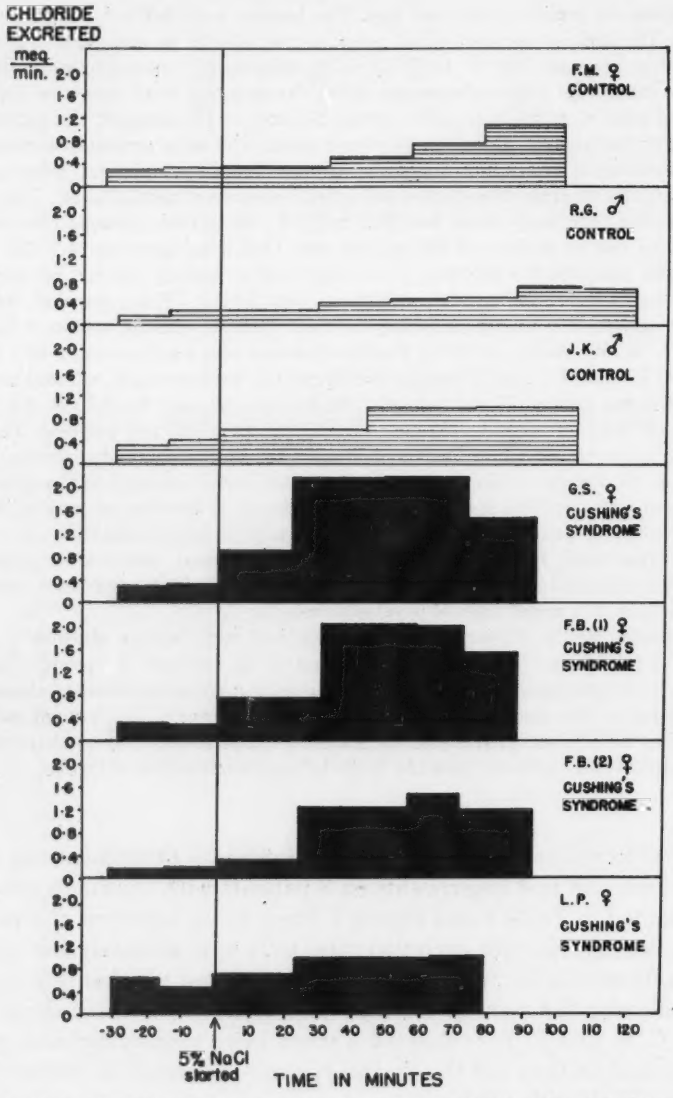

FIG. 1. Rate of renal excretion of chloride before and after the administration of hypertonic sodium chloride, corrected to a standard body surface area of 1.73 square meters.

Renal clearances—All subjects manifested glomerular filtration rates in the normal range (6) or close to the lower limits thereof (Table 1). As reported by others in similar patients (16), the renal blood flow was ab-

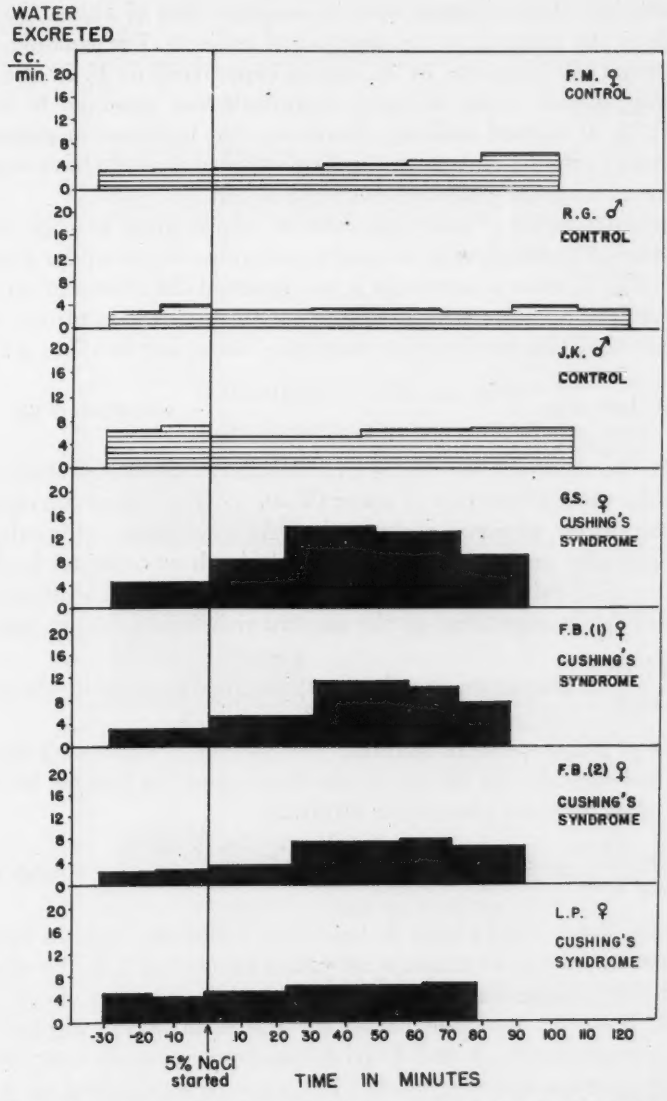

FIG. 2. Rate of renal excretion of water before and after the administration of hypertonic sodium chloride, corrected to a standard body surface area of 1.73 square meters.

normally low in patient G. S. (*see* case report) and probably also in L. P.; both of these patients manifested Cushing's syndrome. There was a tendency for both the mannitol and PAH clearances to rise following the injec-

tion of salt, but these changes were inconsistent and of about the same magnitude in the controls as in experimental subjects. For example, while the glomerular filtration rate in the second experiment on F. B. rose after the injection of salt, a rise of equal magnitude was observed in control subject F. M. It seemed unlikely, therefore, that increases in glomerular filtration rate in the patients with Cushing's syndrome could have been the only factor causing the excessive excretion of salt.

Tubular reabsorption of water and chloride—An attempt is made here to express chloride excretion rates at comparable rates of glomerular filtration and urine flow in order to ascertain if the observed differences in excretion may be ascribed to differences in degrees of tubular reabsorption. On the assumption that mannitol is not reabsorbed from the tubules, we have employed the ratio $\frac{\text{urine mannitol concentration}}{\text{plasma mannitol concentration}}$, designated as "mannitol U/P," to represent the degree to which the glomerular filtrate is concentrated by the reabsorption of water (Table 1). The higher the ratio, the greater the degree of water reabsorption. As a corollary, any substance which is partially reabsorbed by the tubules (such as chloride) is characterized by a U/P ratio less than the simultaneous mannitol U/P ratio, the discrepancy being dependent on the amount reabsorbed. Hence, the ratio $\frac{\text{mannitol U/P}}{\text{chloride U/P}}$ is always greater than 1.0; the higher the ratio, the greater the degree of reabsorption of chloride. This method of expressing degree of chloride reabsorption has the advantage that correction is made for differences in urine flow and glomerular filtration.

$\frac{\text{Mannitol U/P}}{\text{Chloride U/P}}$ ratios throughout all clearance periods for 5 subjects are presented in Table 1 and Figure 3. Analytical difficulties with the mannitol determination prevent inclusion of all values for control J. K. As would be expected, this ratio declined in all subjects after the injection of salt. It will be noted, however, that the values for the ratio in the patients with Cushing's syndrome (G. S. and F. B) dropped precipitously after the start of the salt injection and soon reached low levels never attained by the control subjects. We interpret these findings as indicating an abnormally pronounced diminution of chloride reabsorption in the renal tubules of these 2 patients with Cushing's syndrome when a large "salt load" was imposed.

In the third patient, L. P., the ratio $\frac{\text{mannitol U/P}}{\text{chloride U/P}}$ was initially relatively

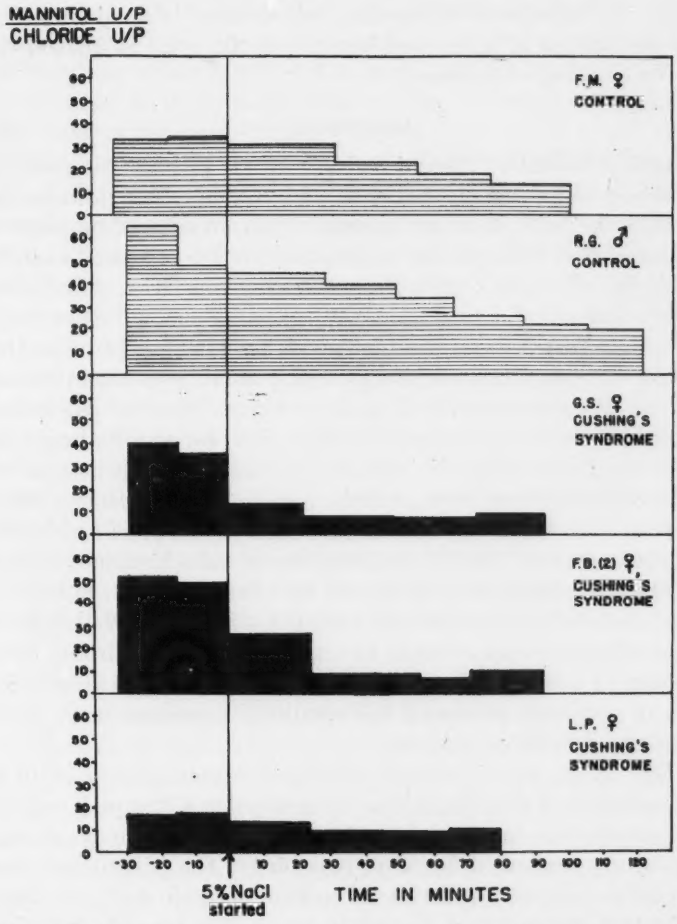

FIG. 3. Chloride reabsorption ratios before and after the administration of hypertonic sodium chloride. The ratios in periods 4, 5, and 6 in the experiment on G. S. and in the first experiment on F. B. are to be regarded as maximum values and higher than the true figures.

low and consequently its subsequent fall to very low levels appeared less striking.

It will be noted (Table 1) that the mannitol U/P ratio observed in the patients with Cushing's syndrome became considerably lower after the salt was administered as compared to the pre-injection levels. In contrast, this ratio in the control subjects showed only slight decreases or no change as compared to the pre-injection levels. We interpret these findings as indi-

cating that the injection of hypertonic salt resulted in an abnormally pronounced diminution of water reabsorption in the renal tubules of the patients with Cushing's syndrome.

DISCUSSION

Our findings resemble those of Soffer *et al.* (4) in suggesting that under certain circumstances some patients with Cushing's syndrome excrete sodium chloride (salt) in larger amounts than do control subjects. Soffer has suggested that one possible explanation for the increased excretion of salt by his patients with Cushing's syndrome given DCA, may be conversion of the injected DCA into a non-salt-retaining, or "salt-excreting" hormone. Since at least 2 of our 3 patients with Cushing's syndrome exhibited a relatively increased diuresis of salt under conditions *not* involving administration of exogenous DCA, such an explanation for our findings is impossible. We favor the possible explanation, for our findings, that in Cushing's syndrome there is increased production of hormones of the 17-hydroxycorticosterone type, which, though predominantly "carbohydrate-active," also have "salt-excreting" effects (17), presumably through an inhibition of renal tubular reabsorption of salt. Evidence supporting such increased production is the report that in Cushing's syndrome there occurs an abnormally high urinary excretion of substances thought to be 21-carbon adrenocortical steroids having a ketone or hydroxyl group on carbon atom 11 and an hydroxyl group on the 17th carbon atom (18). The influence of naturally produced salt-retaining hormones may, therefore, be overbalanced in these patients.

In patient F. B., with Cushing's syndrome, administration of 10 mg. of DCA according to Soffer's technique (4) resulted in a "normal" salt-retaining response despite the fact that she exhibited salt diuresis during our clearance study performed five days previously. The patient had been fed a measured diet supplying 8 Gm. of sodium chloride daily for two days before the test was initiated. In this instance, it is possible that the salt-retaining effect of 10 mg. of DCA was sufficient to overcome any salt-excreting effect of the patient's own adrenal hormones. Soffer (19) has also found that some patients with Cushing's syndrome give a normal response to the test. A similar variability of response of patients with Cushing's syndrome to salt-excretion tests is exemplified by the results recorded for our patient L. P. This patient differed from our other 2 abnormal subjects in that the output of chloride in the control period was greater; and probably, in part as a result of this, the responses to the injection of hypertonic sodium chloride solution were less striking. As an explanation for such variations in response, the possibly significant effect of variations in salt intake preceding the experiments cannot be excluded. Additional study of this factor in both normal subjects and in patients is desirable. Further-

more, it is not to be expected that all patients classified as manifesting "Cushing's syndrome" are identical in their physiologic status. Thus, no two of the three patients referred to herein as manifesting the syndrome appeared either on gross inspection or after laboratory investigation to manifest exactly the same disease-complex.

We have further observed in 2 obese females with arterial hypertension that the Soffer tests was positive for Cushing's syndrome at the time of menstruation and negative in the same patients in the intermenstrual period.[5] The 2 patients had subsisted on a measured diet supplying 8 Gm. of salt daily for at least six days before each test. During the intermenstrual and premenstrual periods, the urinary excretion and presumably the blood concentration of estrogenic substances is relatively great, and at these times in the sexual cycle there occurs a retention of salt and water (20). Salt retention has also been demonstrated to occur following the administration of estrone, α-estradiol, and progesterone (21). At the onset of the menses, excretion of substances of ovarian and luteal origin decreases precipitously and there occurs a concomitant increase in excretion of sodium and chloride (20). In contrast to the marked cyclical fluctuations in the urinary excretion of estrogenic substances, the excretion of "carbohydrate-active" corticosteroids is relatively constant throughout all phases of the sexual cycle (22). Hence, during the catamenia, the ratio

$$\frac{\text{blood corticosteroid content}}{\text{blood estrogen content}}$$

is probably greater than at any other time during the sexual cycle. Such a temporary preponderance of adrenocortical influence may possibly account for the observed positive response to a test for hypercorticoadrenalism such as the Soffer test. With the rise in estrogen production which occurs after menstruation, the hormonal interrelationships may be so adjusted that the salt-retaining effects of the estrogenic and luteal hormones predominate over the salt-excreting effects of the corticosteroids; at this time the Soffer test might be expected to be negative. It is impossible for us to explain why DCA produced the observed *increased* excretion of salt in Cushing's syndrome (4) and during menstruation in our 2 obese subjects with hypertension.

One of our patients with Cushing's syndrome (G. S.) who excreted injected salt unusually rapidly, exhibited marked abnormalities in the serum electrolyte pattern resembling those previously described by Willson, Power and Kepler (23). Another patient with Cushing's syndrome (F. B.)

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[5] These 2 patients were hospitalized during the course of an investigation of hypertension supported by the U. S. Public Health Service. We are indebted to Dr. Henry A. Schroeder for the privilege of studying them.

excreted injected salt in a similar manner, although she exhibited a normal serum electrolyte distribution.

Two of our patients with Cushing's syndrome (G. S. and F. B.) underwent a test for diabetes insipidus, performed according to the method of Hickey and Hare (14). Both manifested a normal antidiuretic response to 2.5 per cent sodium chloride solution. Chronically diminished output of the antidiuretic factor of the posterior lobe of the pituitary, therefore, probably does not account for the diuresis of water and chloride which we observed. In this connection, it is of interest that the test of Hickey and Hare resembles in many aspects the procedure which we have described under "Methods," save that we did not establish the marked diuresis in the control periods which their test (14) entails.

As we have already indicated, the diminished degree of chloride and water reabsorption observed in at least 2 of our patients with Cushing's syndrome is very possibly due to an imbalance of adrenal hormones or hormonal byproducts influencing the renal tubular epithelium. Although we regard this as the most likely explanation, we have no incontrovertible evidence that this mechanism actually occurs. Another explanation, which we regard as less likely, is that the co-existing hypertension and slight renal ischemia in the patients with Cushing's syndrome so altered tubular function as to prevent a normal degree of reabsorption of chloride. We also cannot completely exclude the possibility that increases in glomerular filtration rate and consequent increased rate of flow of the glomerular filtrate down the tubules may have been partially responsible for the observed diminution in the degree of tubular reabsorption of chloride.

SUMMARY AND CONCLUSIONS

1. The renal excretion of chloride, water, mannitol and para-aminohippurate has been measured before, during, and after the rapid intravenous injection of a "salt load" of 20 grams of sodium chloride in 3 controls and in 3 patients with Cushing's syndrome.

2. Following the injection of sodium chloride, the rate of excretion of chloride, sodium, and water by 2 of the 3 patients with Cushing's syndrome exceeded that observed in the control subjects.

3. The increased excretion of chloride and water by 2 of the 3 patients with Cushing's syndrome was accompanied by a diminished degree of renal tubular reabsorption of these substances as compared to the controls.

Acknowledgments

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GRAVES' DISEASE: TREATMENT WITH RADIOIODINE (I^{131})*†

MAYO H. SOLEY, M.D.,‡ EARL R. MILLER, M.D. AND NADINE FOREMAN, M.D.§

From the Divisions of Medicine and Radiology of the University of California Medical School and the Thyroid Clinic of the University of California Hospital, San Francisco, California

CARRIER-FREE I^{131} has been administered by us to patients with Graves' disease since August 1944 in order to study primarily: a) the efficiency of I^{131} as an agent employed to destroy hyperfunctioning thyroids subtotally; and b) the uptake of iodine by the thyroid before and after those symptoms of hyperfunction of the thyroid associated with Graves' disease have been relieved (1).

Up to the time of writing this summary, 68 patients with Graves' disease have been studied and sufficient data are available to permit reporting results in 46 patients. All these patients had undoubted Graves' disease varying in degree from mild to severe; the majority had moderately enlarged thyroids, moderate hyperthyroidism and (with one exception) no nodules in the thyroid. In the initial phases of this study, small (250 microcuries) doses of radioactive iodine were given at weekly intervals; later more adequate single doses of 1000 to 4000 microcuries were given and repeated as necessary up to a total dose as high as 10,411 microcuries.

Prior to the studies on humans, the effects of I^{131} were studied in animals. Three hundred microcuries per kilogram were injected subcutaneously into rabbits and dogs. At the end of ten days, the rabbit thyroids showed extensive necrosis, hemorrhage, polymorphonuclear infiltration and arterial changes. By the twentieth day other rabbit thyroids still had polymorphonuclear plus eosinophilic and lymphocytic infiltration, healing vascular changes and fibrosis. At the end of thirty and forty days, further fibrosis

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‡ Present address: University of Iowa College of Medicine, Iowa City, Ia.

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had occurred; the thyroid had decreased approximately 50 per cent in size; and arteries had intimal and medial fibrosis, thickening and perivascular fibrosis. Only a few questionably normal acini remained at the poles. Dog thyroids removed forty days after 300 microcuries per kilogram of I^{131} showed similar changes and after one hundred days the thyroid of one dog was practically completely destroyed. One rabbit showed damage in the renal tubules but the other glands of internal secretion, the trachea, bone marrow, liver, spleen, lymph nodes, kidneys and peripheral blood counts were normal (2). Barker (3) in recent but unpublished work has not found this degree of change in the thyroids of rats sacrificed three to six days after being given 350 microcuries per kilogram of I^{131}; the explanation though not yet clear probably is related to the amount of iodine in the diet of his animals and a lower uptake of iodine by their thyroids. More recently (4) rabbits were given 500 microcuries of I^{131} per pound orally and five days later up to 4000 microcuries per pound orally and were sacrificed at the end of four weeks. The rabbits' thyroids were partially or completely destroyed and in addition, tracheal and renal tubular injury were apparent; no other damage was demonstrable from gross or microscopic examination of tissues. Gorbman (5) has used doses of 3–4 and up to 50–55 millicuries of I^{131} in mice and found 90 per cent destruction of the thyroid and 100 per cent destruction of the parathyroids at the end of one hundred and twenty days even with the lower dosage. Bengt Skanse (6) has shown that doses of I^{131} (50 microcuries or less) definitely decrease the ability of the chick thyroid to take up iodine. It should be pointed out that the largest single dose of I^{131} (measured as microcuries per Kg. of body weight) administered by us to a patient with Graves' disease is one-fourth as large as that required to destroy subtotally the thyroids of normal rabbits (without injuring other tissues) and one-fortieth the dose that destroys the parathyroids of normal mice. As regards total dosage to patients, one-seventeenth of the dose that destroys the parathyroids of mice is the largest amount given to thyrotoxic patients at the University of California.

UPTAKE STUDIES

The maximum amounts of I^{131} taken up by the thyroids of 48 patients with Graves' disease varied from 12.5 to 92 per cent of an orally administered dose before any treatment, with an average of 61 per cent. The lowest figure was found in a patient in partial remission. In patients treated with Lugol's solution or with one of the thiouracils or with both, the uptake varied from 22 per cent to 70 per cent and averaged 48 per cent.

In order to determine the uptake of radioiodine per gram of thyroid tissue, the size of the thyroid was estimated by palpation. In the past it has been the custom in the Thyroid Clinic of the University of California to

palpate the thyroid carefully preoperatively, record the weight as estimated by the clinician and compare this weight with that of the thyroid tissue removed at operation. The same individual (M. H. S.) who has estimated the weights in patients treated with radioiodine has also examined enough thyroids in surgically treated patients to obtain some appraisal of his accuracy. This was done as follows: surgeons doing subtotal thyroidectomies measured the amount of thyroid tissue left *in situ* after a Halsted type of operation by cutting a piece of the removed thyroid tissue equal in size to the tissue left in the patient. The total removed tissue was weighed during the gross examination of the specimen by the pathologist and the weight of the small amount of tissue corresponding to that left in the patient was added to give the total weight of the patient's thyroid. This actual weight has been compared with the clinically estimated weight in 74 patients with toxic goiters. The results of this study indicate that this particular observer (M. H. S.) has in two-thirds of these 74 patients ranged in his estimates from 24 per cent below the actual weight to 13 per cent above; 95 per cent of his estimates ranged from 42 per cent below to 31 per cent above the actual weights. In terms of weight of thyroid tissue, the error in 66 per cent of patients varied from 13 grams below, to 7 grams above the measured weight; while in 95 per cent of the patients the range of error was between 23 grams below and 17 grams above the confirmed weight. While this degree of accuracy was disappointing, it nevertheless probably represents the accuracy to be expected from a conscientious observer. In only 25 per cent of patients were the estimates within 10 per cent of the actual weight.

The weight of the thyroid and the amount of radioiodine in the thyroid must be known in order to determine the radiation to the thyroid. Also obvious is the necessity of recognizing errors in: a) the measurement of the millicurie, b) the measurement of the uptake of radioiodine by the thyroid *in situ*, and c) the estimation of thyroid size. The latter errors have received too little attention. The methods used in measuring the millicurie and the uptake of radioiodine *in situ* have been described previously (1).

The concentration of I^{131} per gram of thyroid tissue was calculated in 44 patients, and ranged from 21.3 to 247.8 microcuries per gram with an average of 77.7 microcuries per gram. Twenty-seven of these patients were in the group classified as having had a satisfactory response, yet the variability of uptake was tremendous since the lowest uptake measured 21.3 and the highest 143.5 microcuries per gram of thyroid with the average at 95.2 microcuries. One patient who was not normal at the end of a year after a total dose of 9750 microcuries had an uptake of 247.8 microcuries per gram. At the other extreme, two patients who developed frank myxedema had an uptake of 43.5 and 47.5 microcuries per gram respectively.

Thus the evidence presented indicates that many factors other than the concentration of I^{131} are active in determining the amount of I^{131} needed to produce a satisfactory remission in a patient with Graves' disease.

RESULTS

A patient is considered to have responded satisfactorily to treatment by I^{131} if within approximately four months the signs and symptoms of thyrotoxicosis have disappeared, the thyroid has returned to normal size and the basal metabolic rate, level of serum protein-bound iodine and other laboratory findings are within normal limits. Forty-two patients fall into this category. The data are summarized in Table 1. Complete data on the first 25 of these patients have been published (1); the added 17 patients differ in no material way from the original 25.

TABLE 1. SATISFACTORY RESULTS OF I^{131} THERAPY IN 42 PATIENTS WITH GRAVES' DISEASE (4/16/48).

	Before treatment	After treatment
Basal metabolic rate	plus 27.7%*	minus 6.7%
Protein-bound iodine (serum)	9.7 micrograms %	6.2 micrograms %
Estimated weight of thyroid	29 grams	12 grams
Total dose I^{131}: 3017 microcuries		
Time to return to normal: 3.35 months		

* Mean values.

Four patients fail to satisfy the criteria for a satisfactory response in the sense that the interval between the beginning of therapy and the return to normality was prolonged, as shown in Table 2. These four patients had larger thyroids, more severe hyperthyroidism (as measured by their clinical

TABLE 2. SLOW RESULTS OF I^{131} THERAPY IN 4 PATIENTS WITH GRAVES' DISEASE (4/19/48).

	Before treatment	After treatment
Basal metabolic rate	plus 47%*	minus 4%
Protein-bound iodine (serum)	12.9 micrograms %	5.8 micrograms %
Estimated weight of thyroid	38 grams	15 grams
Total dose I^{131}: 4838 microcuries		
Time to return to normal: 14.5 months		

* Mean values.

status, basal metabolic rates and serum protein-bound iodine) and required larger doses of radioiodine as well as a longer time to return to normal.

In addition to the 46 patients described in Tables 1 and 2, two more were subjected to subtotal thyroidectomy. One was done because of poor cooperation and the other because of a poor response to radioiodine therapy and subsequent evidence that she had a nodular goiter. Three more patients have not returned to normal and eventually if and when they do return to normal, will be classified as "slow responses"; five have not returned to the clinic sufficiently often nor recently enough to allow adequate appraisal. One more has become pregnant so that determination of her status in any precise way is difficult. Finally, 11 of our 68 patients have been followed for too short a time after therapy to allow proper evaluation at this date. The slow results and failures can be accounted for in the main by our too conservative dose schedules in the early days and inability to obtain enough radioiodine to give as large doses as were thought necessary.

Some of the clinical and laboratory findings in these patients were of interest. Not infrequently tenderness in the thyroid region was noted within twenty-four to seventy-two hours after I^{131} had been given. It was sometimes noted spontaneously by the patient and was nearly always apparent on palpation, especially when 2000 or more microcuries were given in a single dose. During this period of tenderness in the thyroid, the blood sedimentation rate increased to as high as 35 mm. (Wintrobe); also the protein-bound iodine rose temporarily and was sometimes associated with an increase in the signs and symptoms of hyperthyroidism between the fourth and tenth days.

The eyes of 47 patients were measured with a Hertel (Zeiss) ophthalmometer in order to record changes in prominence during and after radioiodine therapy. There was no significant change in 31 patients. In 12 patients an increase of 1.5 to 2.0 millimeters was noted. In 4 individuals the increase in exophthalmos was greater than 2 millimeters and actually was 5 millimeters in one; three of the four were classified as having severe progressive exophthalmos. The 3 patients with severe exophthalmos were treated with thyroid to tolerance, and in one there was a regression of 1 millimeter in the right eye and 2 millimeters in the left eye after a period of nine months. Thus 66 per cent of patients showed no change in the prominence of their eyes, 25.5 per cent showed a definite but minimal increase and 8.5 per cent had a marked increase. In our experience an increase in exophthalmos occurs less frequently than in surgically treated patients and more frequently than in patients treated with x-ray. The significance of these findings must await further experience.

Fifteen patients who had had Graves' disease had uptake studies repeated after therapy with I^{131}. The results in eleven of these patients were

within the normal range, with an average uptake of 16.6 per cent of a test dose of I^{131} (range: 2.5 to 25 per cent). Four patients who had been treated and who were in the lower normal range as regards their thyroid status, yet who could not be defined as having frank hypothyroidism, showed an interesting phenomenon in that their thyroids took up 3, 46, 49, and 75 per cent respectively of a test dose of I^{131}. A possible explanation of the high uptake in 3 of these patients is that so much of the thyroid had been destroyed that the small remnant was overfunctioning in the sense of utilizing more iodine in an attempt to produce enough thyroid hormone to maintain the patient in a normal thyroid state.

COMPLICATIONS

Two patients became myxedematous after therapy. The first was a woman with only moderate hyperthyroidism whose basal metabolic rate was plus 26 per cent and serum protein-bound iodine 9.6 micrograms per cent, whose estimated 25 gram thyroid took up 49 per cent of her therapeutic dose of 2250 microcuries of I^{131}. The second patient was a woman with somewhat more marked hyperthyroidism with a basal metabolic rate of plus 38 per cent and serum protein-bound iodine of 9.9 micrograms per cent, whose 35 gram thyroid took up 75 per cent of her therapeutic dose of 4000 microcuries of I^{131}. Both patients developed myxedema a few weeks after therapy, in the same manner as does the patient with treated myxedema who exhibits symptoms and signs of recurring myxedema when thyroid therapy is discontinued. The doses of I^{131} of only 43.5 and 47.5 microcuries of I^{131} per gram of thyroid respectively were apparently large enough to inhibit completely the production of thyroid hormone. Not enough time has elapsed to permit us to be sure that the destruction of the thyroids in these two patients is complete and permanent or whether some function will be regained in the future.

COMMENT

Disagreement still exists among groups of workers using I^{131} regarding selection of patients for therapy, dose to be employed and the advisability of a single large dose rather than several smaller doses (7, 8). Differences of 30 to 50 per cent or more in the measurement of aliquot fractions of I^{131} persist from one laboratory to another. Only time will permit resolution of some of these problems and even then there will remain different but adequate doses and dose schedules.

SUMMARY

The results of treatment of 46 thyrotoxic patients with radioiodine over the period from 1944 to 1948 are presented, in which there were 42 satis-

factory responses and 4 unsatisfactory responses. The latter are felt to be due to a conservative approach to therapy in the early phases of the study.

Animal experimentation has been carried on to determine the effects of massive doses of I^{131} upon tissues surrounding the thyroid, and the pathologic changes have been described. It has been found that upwards of forty times the maximum therapeutic dose (in microcuries per kilogram) used in humans is required to produce serious damage in contiguous structures in mice and rabbits.

The uptake of radioiodine by the thyroid in untreated Graves' disease was found to average 61 per cent, whereas in the treated patient it averaged 16.6 per cent. There appears to be a paradoxical lack of correlation between clinical response to treatment and the number of microcuries per gram delivered to the thyroid.

I^{131} in doses of 2 millicuries or more causes clinical and laboratory changes that point to tissue destruction (thyroid). After therapy with I^{131} exophthalmos progresses less than in patients treated by subtotal thyroidectomy and more than in patients treated with x-ray. Two patients in this series developed myxedema.

CONCLUSIONS

Radioactive iodine (I^{131}) in adequate dosage will destroy subtotally the hyperfunctioning thyroids in patients with Graves' disease and thereby produce usually a satisfactory remission of the symptoms and signs of hyperthyroidism. Further studies ultimately will disclose its place in the therapy of Graves' disease.

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THE DEVELOPMENT OF DIABETES MELLITUS IN ADDISON'S DISEASE

CASE REPORT WITH AUTOPSY

ABBIE I. KNOWLTON, M.D. AND ROBERT A. KRITZLER, M.D.

From the Departments of Medicine and Pathology, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital in the City of New York

THE occurrence of both adrenal cortical insufficiency and diabetes mellitus in the same individual is rare; reports of only twenty-two such instances are available. Each of these diseases is associated with abnormalities in carbohydrate metabolism in some respects antagonistic to the other and consequently the simultaneous occurrence of the two is of considerable interest.

In the reports reviewed, diabetes was established in the majority of the patients before the development of Addison's disease. (1–12). In four, however, both diseases were recognized simultaneously (13–16), while in three others, (17–19) the adrenal insufficiency antedated the appearance of diabetes.

The presence of adrenal cortical hypofunction frequently alters the coexisting diabetic state. A number of these patients are reported to exhibit an unusual sensitivity to insulin (1, 3, 5, 8, 13, 14, 15, 18, 19) such as is characteristically found in Addison's disease alone. Severe hypoglycemic reactions are commonly mentioned and, in those patients with pre-existing diabetes, a fall in insulin requirement frequently follows the development of hypoadrenalism (4, 6, 8, 9, 10). However, in one instance, the daily dosage of insulin is reported unchanged (7), following the appearance of adrenal insufficiency and in ten others, either insufficient evidence is presented to establish this point or no reference is made to this problem.

The effect of adrenal replacement therapy on the coexistent diabetic state varies with the substances employed. When desoxycorticosterone acetate (DCA) has been used, no change has been reported. This is consistent with experimental evidence indicating that this steroid plays a negligible role in carbohydrate metabolism. On the other hand, the available evidence indicates that extracts of the whole gland and more strikingly the C-11 oxy-steroids may lead to an increased glycosuria and possibly greater insulin requirement in the diabetic Addisonian patient. The first report suggesting this action of the whole gland extract is Levy-Simpson's in 1932 (14). His patient entered the hospital in a state of adrenal insufficiency with hypoglycemia and the underlying diabetic state became ap-

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parent only after nineteen days of adrenal cortical extract therapy. However, the increased food intake due to control of the adrenal insufficiency may also have been a factor here. Later, Bloomfield (4), Bickel (8) and Bowen, Koepf, Bissell and Hall (6) noted higher blood sugars during fasting when their patients were receiving extracts of whole adrenal gland than when DCA was employed, and Soffer (12) thought that the insulin requirement of his patient was greater under similar circumstances. Thorn and Clinton (18) and Sprague and co-workers (11) observed a marked increase in glycosuria and nitrogen excretion following the administration of 11-dehydro-17-hydroxycorticosterone (compound E), and in addition the latter authors reported similar though less striking responses to hog adrenal extract (lipo-adrenal cortex) and in one instance to 11-dehydrocorticosterone (compound A).

The present report concerns a third patient in whom diabetes mellitus with striking insulin sensitivity appeared two and one-half years *after* the diagnosis of Addison's disease was established.

CASE HISTORY

E.G. was a 22-year-old single woman who was first admitted to the Presbyterian Hospital in July 1942 for evaluation of suspected Addison's disease. Her initial symptoms appeared six years previously, at which time she began to have bouts of nausea and vomiting occasionally accompanied by fainting during her menstrual periods. It was not until three years later that increasing pigmentation of her skin become evident, and in the ensuing year she became aware of increasing fatiguability and a decrease in appetite which led to a 7-pound weight loss. One year before admission to this hospital she went to the Mayo Clinic, where a Cutler-Power-Wilder test, though somewhat equivocal, was on the whole in keeping with the diagnosis of Addison's disease. Subsequently the addition of 10 grams of sodium chloride a day to her diet led to a definite improvement in her symptoms.

There was no history of known exposure to tuberculosis. It is of interest that a paternal aunt died of diabetes.

Physical Examination: On admission in July of 1942, she was a thin, intelligent young woman who looked chronically ill. There was a diffuse muddy pigmentation of the skin, a few inky black moles, and there were bluish spots on the gums. Her blood pressure was 95/65, temperature 99.8° and pulse 84. The heart was not enlarged; the regular rhythm was interspersed with runs of extrasystoles. The remainder of the physical examination revealed nothing abnormal.

Initial laboratory findings: Hemoglobin 14.5 Gm. per 100 cc.; red blood cells 4,360,000; white blood cells 5,850; polymorphonuclears 52 per cent, lymphocytes 38 per cent, monocytes 4 per cent, eosinophiles 5 per cent, basophiles 1 per cent; erythrocyte sedimentation rate 17 millimeters in one hour.

The urine specific gravity was 1.017; there was no albumin, glucose, acetone or diacetic acid and no formed elements microscopically.

X-ray examination showed a normal chest and skull and no evidence of calcification in the adrenal area.

A tuberculin test was negative in a 1:100,000 dilution; the basal metabolism was

minus 14 per cent; 24-hour excretion of 17-ketosteroids in the urine was 1.5 mg.; and an electrocardiogram showed no evidence of heart muscle damage.

The serum nonprotein nitrogen was 37 mg. per cent and total protein, 6.2 Gm. per cent; blood sugar (fasting), 86, 80 and 74 mg. per cent on three separate occasions; serum carbon dioxide content, 27.4 mEq. per liter; serum chlorides, 100.6 mEq. per liter. The calculated concentration of serum sodium was 138 mEq. per liter, and the direct gravimetric serum sodium, 137.7 mEq. per liter.

Course: When placed on a regimen of salt restriction, she lost 2 kilograms in five days and became anorexic, weak and dizzy. The blood pressure fell to 75/55 and the serum sodium (gravimetric) fell to 132.5 mEq. per liter. With this evidence for adrenal cortical insufficiency she was then given desoxycorticosterone acetate (DCA), by subcutaneous

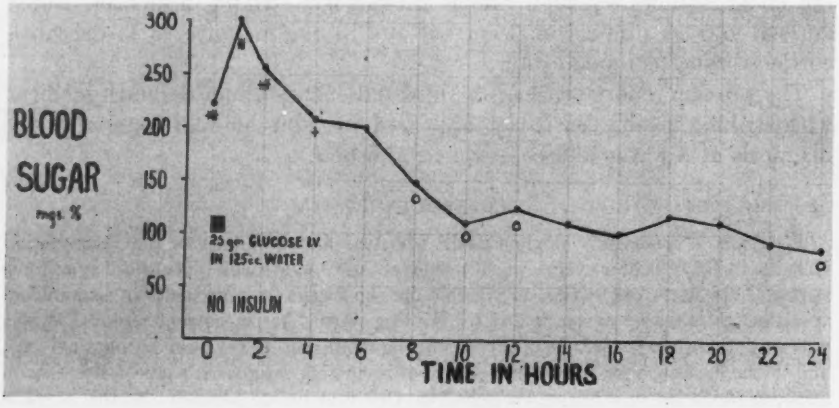

FIG. 1. Blood sugar curve following an intravenous glucose-tolerance test with subsequent 24-hour fast. Urine glucose (O to ++++) at 0, 1, 2, 4, 8, 10, 12 and 24 hours is shown directly beneath corresponding blood sugar values.

injection. In a week and half she gained 3 kilograms and was discharged taking 4 mg. a day without added sodium chloride.

Over the next fifteen months her general condition was satisfactory and serum electrolyte values were maintained within normal limits on the above dosage with an unrestricted diet to which 4 grams of sodium chloride was added daily in the form of enteric-coated tablets. A postprandial blood sugar, three months after discharge, was 67 mg. per cent. Twelve months later, she reported she had had a weak spell associated with mental confusion, which responded promptly to administration of orange juice. Because of this her blood sugar was again checked two months after this episode and was, surprisingly, found to be 308 mg. per cent. With this she had a severe glycosuria (4 plus) though no acetonuria.

In the ensuing three months she was admitted to the hospital twice for regulation of the diabetes and during this time the following studies were done: Initially she was given a diet containing 140 Gm. carbohydrate, 80 Gm. protein and 65 Gm. fat. She received no insulin and the daily amount of glycosuria was determined. On day one, 71 Gm. of glucose was excreted; on days three and four, 94 and 91 Gm. respectively. A

blood sugar, taken during fasting, on the sixth morning of this regimen was 174 mg. per cent. In spite of the severity of the glycosuria, a 24-hour fast without insulin resulted in a disappearance of both glycosuria and hyperglycemia (Fig. 1).

In attempting regulation of the diabetes it was found that extraordinarily small amounts of insulin were sufficient to control the heavy glycosuria and that an additional 1 or 2 units resulted in severe hypoglycemic episodes. Thus, 4 units of standard insulin given before breakfast and before supper was sufficient to maintain adequate control of the diabetes on a diet of 190 Gm. carbohydrate, 100 Gm. protein and 80 Gm. fat.

During this 3-month period, her clinical condition remained good and, with the exception of a drop in sodium to 131.9 mEq. per liter during the period of severe glycosuria, her serum electrolytes remained normal, and the maintenance dose of 3 to 5 mg. of DCA plus 2 to 4 Gm. of sodium chloride was continued.

After this, her third admission, she remained in fairly good health for the next two years, though never strong enough to do more than help out with the lighter chores at home. She maintained the same diet and her insulin requirements varied from 2 to 6 units twice daily. In order to reduce the number of daily injections, her adrenal disease was controlled during this period with subcutaneous implantation of pellets of DCA, inserted at approximately yearly intervals. In the course of these two years she was hospitalized five times for intercurrent infections or for DCA pellet implantations.

Her final, and ninth, admission was in January 1946 for an acute illness of twelve hours' duration beginning with sore throat, weakness, chills and fever. Her temperature on arrival was 103.2°, pulse 100, respirations 18 and blood pressure 96/55. She was acutely ill, lethargic and dehydrated with evidences of a mild upper respiratory infection. The pharynx was not acutely inflamed. Aside from the previously observed pigmentary changes, the rest of the physical examination was entirely normal.

Subsequent laboratory findings: Hemoglobin 12 Gm. per 100 cc.; red count 3,390,000; white count 17,000; polymorphonuclears 75 per cent, lymphocytes 21 per cent, monocytes 3 per cent, basophiles 1 per cent; erythrocyte sedimentation rate 60 mm. in one hour.

Urinalysis showed 4 plus glucose, acetone and diacetic acid, but was otherwise normal.

The blood sugar level (fasting) was 444 mg. per cent. The serum carbon dioxide content was 23.1 mEq. per liter; serum chlorides 95.4 mEq. per liter; serum urea nitrogen 11 mg. per cent; the calculated serum sodium 128.5 mEq. per liter. A throat culture showed hemolytic streptococci but the blood culture showed no growth.

The course of her disease during this admission, with essential laboratory data and therapy, is outlined in Figure 2. When seen initially she was in a state of acute adrenal insufficiency and from this aspect her condition continued to be precarious for the first seventy-two hours, with profound shock, hyperpyrexia and accompanying decreased concentration of serum sodium. During this period she developed generalized muscular rigidity, sufficiently marked in the nuchal region to indicate a lumbar puncture. The results, however, showed a normal spinal fluid. To combat the adrenal insufficiency, she was given both DCA and aqueous whole adrenal extract as well as supportive measures in the form of whole blood, plasma and saline infusions. After the first twenty-four hours the use of the intravenous route was curtailed because she developed signs of fluid retention, namely, facial edema, enlargement of the liver, gallop rhythm, an increase in pulse rate to 120, a rise in venous pressure, rapid respirations (rate 40) and x-ray evidence of pulmonary congestion. Because of these findings she was digitalized on the second day and most of the fluids were subsequently administered by hypodermoclysis.

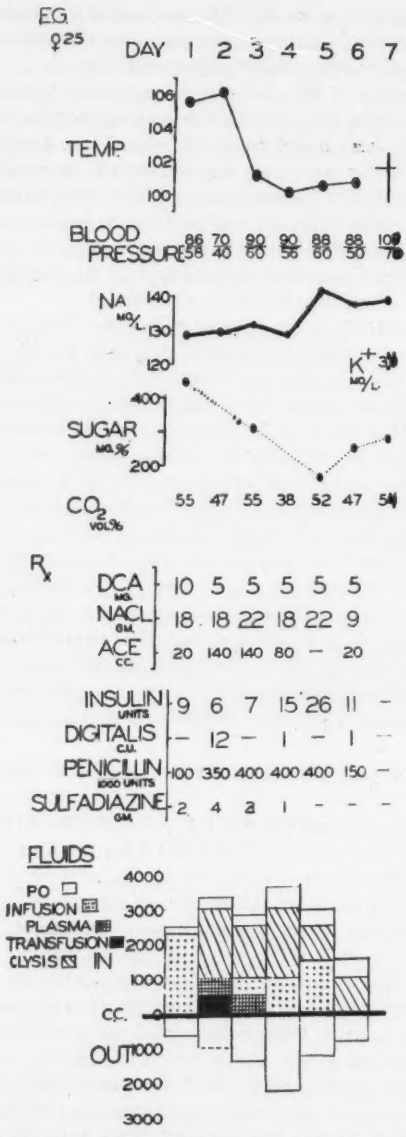

FIG. 2. Chart of clinical and laboratory findings and of therapy employed during final admission of patient E. G.

DCA = desoxycorticosterone acetate

ACE = 10% alcoholic extract of whole adrenal gland.

Her streptococcus infection was treated with both penicillin and sufficient sulfadiazine to maintain an adequate level of this substance in the blood.

On the third day she improved strikingly, but within the following twenty-four hours the diabetes, which on admission had not presented difficulties, became a major problem and she developed moderately severe acidosis. In the first three days no attempt had been made to control the diabetes rigidly, since hypoglycemia seemed the major danger in view of the acute adrenal insufficiency and negligible food intake. Extreme insulin sensitivity persisted; on the first day a total of 9 units effected complete clearing of both acetonuria and glycosuria. Subsequently insulin was given cautiously, in doses of 3 or 4 units, according to the amount of sugar in the urine. On the fourth day, in spite of this, heavy glycosuria persisted and acetonuria appeared with a sharp drop in carbon dioxide content of the serum to 16.2 mEq. per liter. This acidosis cleared with the administration of only 26 units of insulin. At no time during this admission were any hypoglycemic episodes observed.

After the fourth day, the primary problems were pulmonary congestion and the appearance of cardiac arrhythmia. By the fifth day the venous pressure had risen to 195 mm. and x-ray examination of the chest on the following day showed further increase in the pulmonary vascular markings with either bilateral hydrothorax or widespread edema in both lower lobes. A part of the picture was attributed to the fall in serum total protein from the initial level of 6 Gm. to a level of 4.5 Gm. per cent on the fifth day. As to the cardiac arrhythmia, extrasystoles were heard at intervals on the third day. During the fifth night she had a short episode of syncope. The next morning an electrocardiogram revealed varying degrees of A-V block, with low voltage, premature ventricular beats and a marked prolongation of the QT interval. Some of these abnormalities suggested hypocalcemia or hyperkalemia or both. The following night there was a second episode of syncope, with convulsive movements accompanied by asystole. In spite of the repeated administration of adrenalin, four more similar attacks occurred over the next twelve hours; in the last of these, she died.

Final laboratory findings: On the morning of death the blood sugar (fasting) was 278 mg. per cent and the following values were found in serum: carbon dioxide, 22.7 mEq. per liter; chlorides, 106.2 mEq. per liter; urea nitrogen, 6 mg. per cent; calculated sodium, 138.9 mEq. per liter; and potassium, 3.4 mEq. per liter. The urine showed glucose 4 plus and acetone 1 plus, but no diacetic acid.

AUTOPSY

(four hours post mortem)

Gross

The pleural and peritoneal cavities each contained 300–400 cc. of clear fluid. The mesenteric and systemic abdominal veins were distended. The mesenteric and retroperitoneal tissues were more moist than normal. The heart was not enlarged or dilated. It weighed 270 Gm. The myocardium was normal. A small amount of clear fluid was expressed from the cut surfaces of the lungs which weighed 470 and 360 Gm. respectively. No gross abnormalities could be seen in the spleen, liver, gall bladder or kidneys. The pancreas was small, but its normal lobular structure was preserved.

The right adrenal was a gray, wafer-like structure measuring $3 \times 18 \times 0.3$ mm. The left consisted of two 1–2 mm. nodules situated in a thin sheet of fibrous tissue.

A small subserous cyst of the right ovary was filled with clear, yellow fluid. The thyroid was small and its cut surface was gray. Colloid appeared to be reduced. Four

parathyroid glands weighed 143 mg. The bone marrow was slightly pale. The thymus measured 2.5×0.8×0.5 cm.

Microscopic

Heart: In a few small areas of the interventricular septum, the interstitial spaces were widened and the muscle fibers narrowed. There was no necrosis, inflammation or scarring of the myocardium or of the conduction bundle.

Lungs: The interlobular septa, the peribronchial tissue, and the alveoli were mildy edematous.

Liver: The sinusoids in the central zones were mildly congested. Many portal areas were infiltrated by lymphocytes, wandering cells, and polymorphonuclear leukocytes. In sections stained with Best carmine for glycogen, the cytoplasm of liver cells contained an abundance of carminophylic granules, especially in the periportal zone.

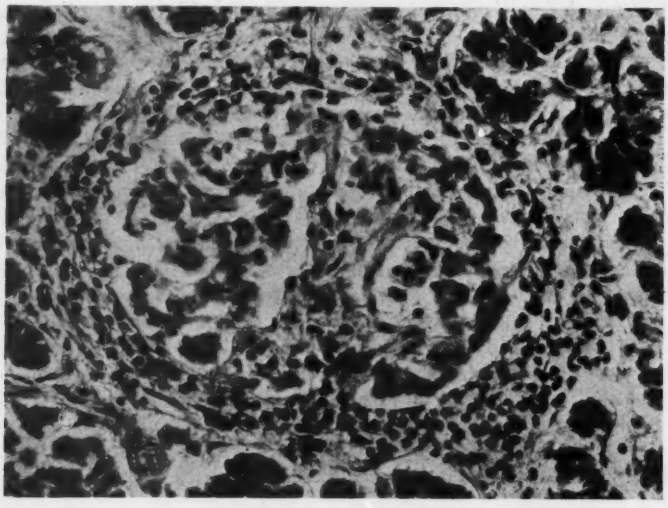

FIG. 3. Pancreas. Tissue around an islet of Langerhans is infiltrated by inflammatory cells. ×360.

Pancreas: Tissue blocks were taken from ten areas. There were small focal areas of infiltration by lymphocytes, and occasional polymorphonuclear leukocytes and fat-laden phagocytes in five. In one section the inflammatory cells infiltrated an islet, (Fig.3). The islets were rather sparse and shrunken. Their cells were very small. The cytoplasm consisted of a very thin rim of dense acidophilic material around small, occasionally pyknotic nuclei. There was no hydropic degeneration, fibrosis, or hyalinization of the islet tissue. Sections from seven blocks fixed in Bouin's solution were stained with chrome hematoxylin phloxin by Dr. George Gomori, of the University of Chicago. No granules were found in any of these (Fig. 4A). Alpha, beta, and delta granules were seen in abundance in islets in sections of pancreas from another case used as a control for the staining technique (Fig. 4B).

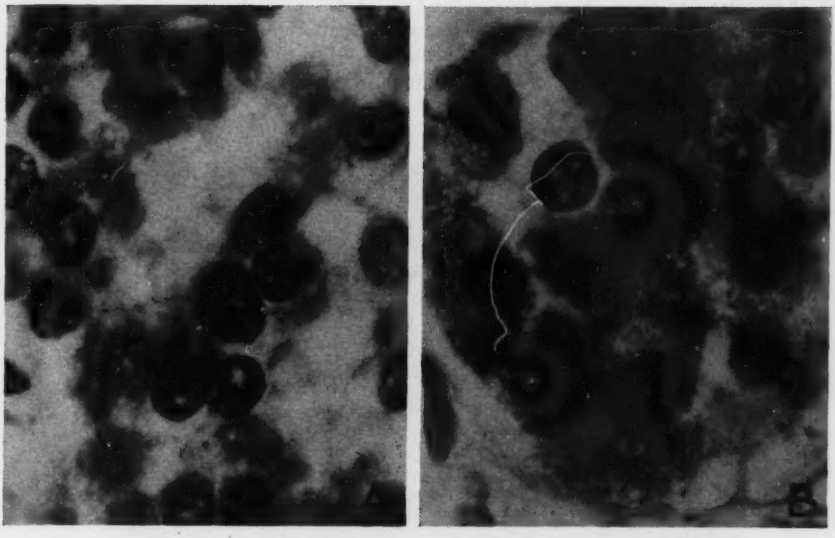

FIG. 4. Cells of the islets of Langerhans. Chrome-hematoxylin-phloxin stain. ×980.
A). From the pancreas of patient E. G. No alpha, beta or delta granules are seen in the cytoplasm.
B) From a normal pancreas serving as a control. Granules are abundant.

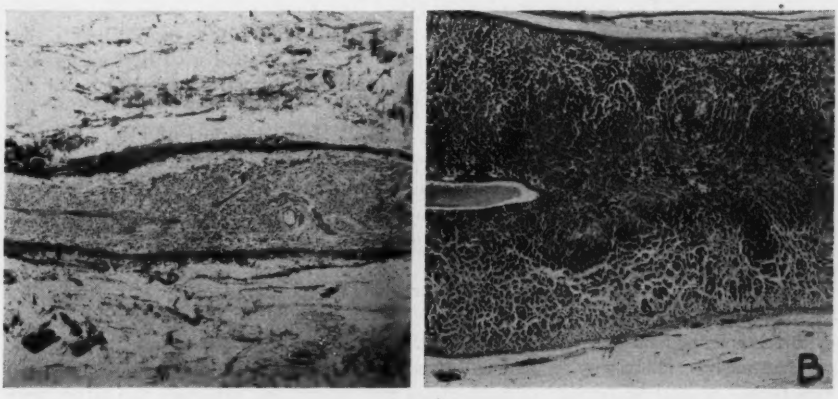

FIG. 5. A) Right adrenal from the patient of this report. Atrophy is advanced. Medullary tissue is absent. B) A normal adrenal for comparison, at the same magnification. ×16.

Adrenals: The right adrenal was about two-thirds of a high power field in thickness (Fig. 5). Within a collapsed, thickened capsule, the tissue consisted of fibrous tissue, collapsed stroma, and a few small groups of atrophied cortical cells, focally infiltrated by lymphocytes. Residual tissue of the left adrenal was even less conspicuous. No medullary tissue was seen in either gland.

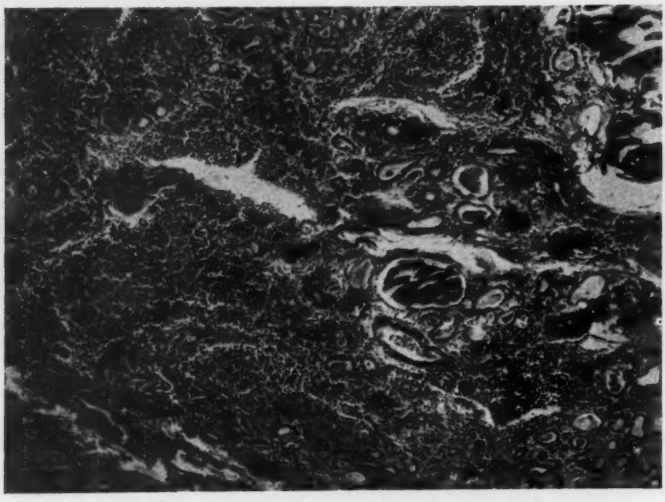

FIG. 6. Thyroid. Atrophy of the follicles in areas infiltrated by lymphocytes. ×80.

Kidneys: There were no abnormal findings. In sections stained with Best carmine, a small amount of carminophylic granules was present in the straight segments of the proximal convoluted tubules and in Henle's loops.

Ovary: This contained a mature Graafian follicle and a corpus luteum cyst.

Uterus: There was cystic glandular hyperplasia of the endometrium.

Thyroid: The major portion of the gland was normal. However, the follicles were atrophied in scattered areas where the tissue was infiltrated by lymphocytes which were occasionally oriented in small follicles (Fig. 6).

Parathyroid glands: These were normal.

Thymus: The thymus was essentially normal. The corticomedullary structure could be distinguished.

Breasts: The glandular tissue was normal. There was marked periacinar fibrosis.

Hypophysis: There was an unusually small number of chromophobe cells, with an apparently normal proportion of acidophiles and basophiles, although the latter were sparsely granulated. There was no frank necrosis, but the presence of pyknosis of nuclei, confluence of cells, breakdown of cell walls, widespread vacuolization of cytoplasm and clumping of cytoplasmic granules in certain areas, adjacent to normal and active cells, was evidence of some degeneration. The presence of such cytologic details as the Golgi

apparatus in the normal cells indicated that the degenerative changes in adjacent cells were probably actual rather than artifacts.

Skin: Melanin was increased in the basal and germinal cell layers.

Brain: (Dr. Abner Wolf) There were no changes of note in the frontal gyrus, the hypothalamus, or in the medulla.

DISCUSSION

The development of diabetes mellitus following Addison's disease is a physiologic paradox of which only three instances other than this patient have been reported. It may be termed a paradox because the expected changes resulting from adrenal cortical insufficiency are in the direction of increased carbohydrate utilization due to the removal of the inhibiting effects of the cortical hormones upon this phase of metabolism. Ingle (20) has established that injections of cortical substances result in a decreased ability to utilize fed glucose. The more recent work of Cori (21) has related this finding to one specific step in carbohydrate breakdown—the conversion of glucuse to glucose-6-phosphate—and has conclusively shown that adrenal extracts, in conjunction with anterior pituitary extracts, exert an inhibitory effect on this reaction. This inhibition is in turn blocked by insulin. Furthermore, since the classical studies of Long and Lukens (22), it has been known that the removal of the inhibitory effect of the adrenals on glucose utilization or on gluconeogenesis by adrenalectomy greatly ameliorates the diabetic state in a previously pancreatectomized animal. It is therefore, somewhat of a paradox that this patient, two and one-half years after known adrenal insufficiency existed, should have developed severe diabetes to the extent of a glycosuria of nearly 100 grams daily.

An unusual sensitivity to exogenous insulin, such as this patient exhibited, has been remarked upon in a number of the previous reports of this dual disease picture and is, of course, known in uncomplicated Addison's disease. It has, too, its experimental counterpart in the adrenalectomized, pancreatectomized animal and is also observed after hypophysectomy. Explanations of this sensitivity, taking into account what is known of insulin action and of "anti-insulins," remain unsatisfactory. The action of insulin described by Cori does not, as he himself has pointed out, explain this observed sensitivity. Recently, in addition to its role in glucose utilization in the liver, a peripheral site of insulin action has been suggested by Perlmutter and Greep (23). These authors reported that the addition of insulin led to an increased glucose uptake in the striated muscle of hypophysectomized as well as of normal rats. Whether the insulin sensitivity in this patient can be related to such a peripheral action of insulin can not be said at present, since the effect of adrenalectomy on this action has not yet been examined.

In all, the explanation of insulin sensitivity such as this patient, in common with other similar cases, exhibited remains unsatisfactory. Recent observations (24, 25) suggest that in addition to the pituitary and the adrenal so-called "anti-insulins," an anti-insulin may be elaborated by the pancreas. It is conceivable that the total absence of granules in the pancreatic islets in the patient here described might indicate the lack of the normal anti-insulin of this region, and in part account for her sensitivity to exogenous insulin. Against this argument are the histologic findings on one other patient with diabetes mellitus and Addison's disease, recently reported by Bernstein (26). In Bloomfield's (4) original description of this patient a marked fall in insulin requirement was noted when Addison's disease supervened. At autopsy Bernstein observed, in Gomori-stain specimens of the pancreas, that "alpha cells were easily recognizable, but only a few unequivocal beta cells were present."

SUMMARY

1. The fourth case of Addison's disease with subsequent appearance of diabetes mellitus is reported.

2. The patient developed diabetes two and one-half years after the diagnosis of adrenal cortical insufficiency was established.

3. A severe degree of glycosuria (71 to 94 Gm. per day) existed in the absence of insulin therapy; however, this glycosuria was controlled with a total of only 6 to 8 units of insulin a day and extreme sensitivity to minute changes in dosage was observed. A 24-hour fast resulted in disappearance of the diabetic state.

4. Autopsy showed: a) complete absence of alpha, beta and delta granules in the islets of the pancreas and unusually small islet cells, and b) marked atrophy of both adrenals with associated lymphocytic infiltrations in the thyroid and liver.

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SURVEY OF A SCOTTISH DIABETIC CLINIC

A STUDY OF THE ETIOLOGY OF DIABETES MELLITUS

H. N. MUNRO, M.B., Ch.B.,* J. C. EATON, M.B., Ch.B.**
AND A. GLEN, M.D.

From the Metabolic Clinic, the Victoria Infirmary, Glasgow, Scotland

DURING the present century statistical information has frequently been gathered from patients attending diabetic clinics, mostly in America. The value of these surveys depends chiefly on the extent to which they can be used in studying the etiology of diabetes mellitus. Greater knowledge of the circumstances under which diabetes occurs in man will permit the important advances which have recently been made in the experimental production of diabetes in animals to be placed more readily in their proper perspective. In carrying out a survey of diabetics seen at a Scottish hospital we have accordingly limited ourselves to a consideration of factors associated with the onset of the disease, *viz.* the incidence of diabetes according to age and sex, the frequency of diabetes in married and unmarried women, the body weight of diabetics prior to the onset of the disease, the blood pressure of diabetics, the hereditary factor in diabetes, and the associaton of diabetes with other endocrine and nonendocrine diseases. The data have been treated statistically. Means are given with their standard errors, and probabilities of less than 0.05 have been accepted as significant.

CLINICAL MATERIAL

The survey is based on the clinical records of 1309 cases of diabetes seen at the outpatient department and in the wards of the Victoria Infirmary, Glasgow during the 10-year period from the inception of a metabolic clinic early in 1932 until February 1942. The following data are relevant to this clinical material:

a) Situation of the hospital. The infirmary serves southern Glasgow and neighbourhood, an industrial area whose inhabitants have an age distribution slightly different from that of Scottish people as a whole: in 1931, 31.3 per cent of men and 31.8 per cent of women in Glasgow were 40 years of age or older, as compared with 32.3 per cent and 34.6 per cent respectively for Scotland. There are also minor racial differences between Glasgow and the rest of Scotland. In this connection only persons of either Jewish or Irish origin need be considered, since a high incidence of diabetes is known

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* Present address: Biochemistry Department, the University, Glasgow, Scotland.
** Present address: Biochemical Department, Royal Infirmary, Glasgow.

to occur among them (1, 2). The size of the Jewish community cannot seriously affect the issue, for only 4.8 per cent of our diabetic cases were Jews. The last census of Scotland (1931) revealed that 2.58 per cent of the Scottish population had been born in Ireland, whereas in Glasgow 4.81 per cent were Irish-born. Thus any differences that may exist between the inhabitants of Glasgow and Scottish people as a whole cannot be important, and we shall later present evidence which suggests that our cases are probably a representative sample of Scottish diabetics.

b) Diagnostic criteria. In most cases the diagnosis of diabetes has been based on a typical history supported by a single blood sugar determination made at random on the patient's first visit to the hospital. Doubtful cases were investigated by a glucose tolerance test (50 Gm. glucose orally): using Hagedorn and Jensen's technique on capillary blood, diabetes was considered to be present when the peak of the curve exceeded 190 mg. glucose per 100 ml. of blood and the return to the fasting level was delayed. Some clinicians have suggested higher blood-sugar values as critical levels for the diagnosis of diabetes: thus Joslin (1) considers 200 mg. per 100 ml. to be the significant level and Hale-White and Payne (3) suggest 220 mg. for elderly subjects. These differences of opinion are unlikely to vitiate our data, for few of our cases lie within the doubtful zone. In a random sample of 269 case records we found that only 5 per cent of diagnoses had been based on blood-sugar values of less than 200 mg. per 100 ml. of blood and 13 per cent on values of less than 220 mg. (these include single estimations taken at random as well as tolerance-curve peaks).

c) Representative nature of the clinical material. In an attempt to test whether our cases were a representative sample of Scottish diabetics, we compared the ratio of male to female patients at our clinic with the ratio of male to female deaths from diabetes recorded in the official returns of deaths for Scotland. In using mortality statistics for this purpose, it is necessary to show i) that the mortality statistics do not distort the proportion in which male and female diabetics die, and ii) that the ratio of male to female deaths from diabetes remains reasonably constant during the period studied. It can then be assumed that the sex ratio among new cases is the same as the sex ratio found in the mortality statistics, despite the long interval elapsing between onset of diabetes and death.

The first of these conditions was shown to be fulfilled when the death certificates of 128 of our diabetic cases were traced. Although only 67 per cent of these were finally classified as deaths due to diabetes in the Annual Returns of the Registrar-General for Scotland[1], the sex distribution was

[1] This reduction is due to losses of two kinds, a) failure by practitioners to enter diabetes on the death certificate, and b) other coincident diseases taking precedence over diabetes as the classifying cause of death.

very little altered (Table 1). In order to test the second point, the standardized death rates[2] from diabetes during the period 1901–1940 were calculated for men and women separately (Fig. 1). Although the ratio of the female to the male death rate was subject to considerable disturbances up

TABLE 1. AN INVESTIGATION INTO THE CERTIFICATION AND RECORDING OF DEATHS FROM DIABETES IN SCOTLAND

[The certificates and mortality data are classified according to the 1929 revision of the International List of Causes of Death.]

	Total number	Ratio of female to male diabetics in groups	χ^{2*} test
Number of investigated deaths from diabetes	128	2.12:1	
Those classified as deaths from diabetes in the Annual Returns of the Registrar-General for Scotland	86 (67%)	2.19:1	
Annual number of deaths from diabetes recorded in the Returns of the Registrar-General for Scotland (mean for the years 1931–40)	781	2.06:1	
Therefore, estimated true number of deaths from diabetes occurring annually in Scotland	1163	2.00:1	3.67†
New cases seen in clinical practice (authors' clinic, 1932–42)	1309	2.26:1	

* Chi-square, an index of dispersion.

† Sex distribution at clinic not significantly different from sex distribution of deaths among Scottish diabetics during 1931–40.

to 1930, it attained a rather stable plateau after that year. It is therefore probable that the similarity between the sex distribution at our clinic and the sex distribution of deaths among Scottish diabetics during 1931–40

[2] The standardized rate is appropriate here because it allows for changes in the average age of the population during the period studied. On account of the long duration of diabetes in recent years, we have used broad age groups (0–14, 15–34, 35–54 and 55 years upwards) in calculating the standardized rate, which is based on a population of a million persons distributed as was the population of Scotland in 1901.

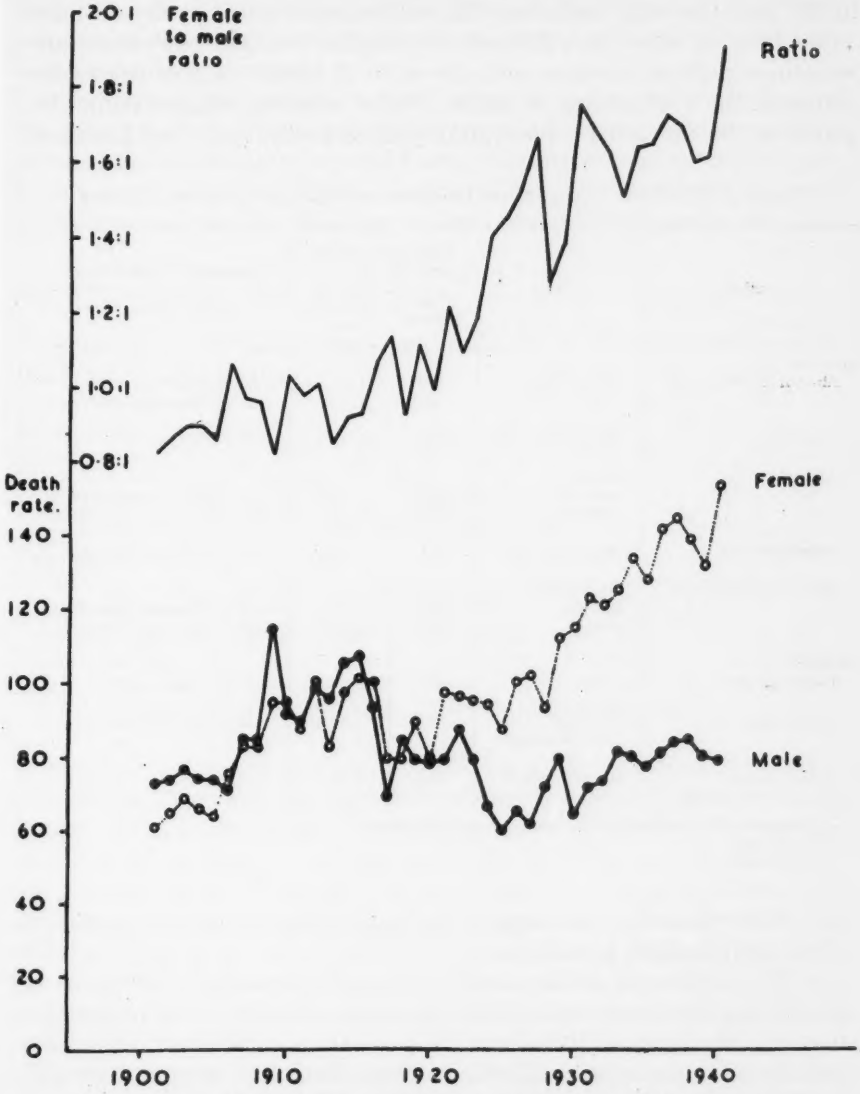

FIG. 1. Standardized death rate from diabetes in Scotland (1901–1940).

(Table 1) is an indication of the representative nature of our clinical material.

Comparisons have also been made (Table 2) between the sex incidence noted at some other clinics and the sex distribution of deaths from diabetes

in the local mortality statistics. The sex incidence noted at these clinics varies from an excess to a deficiency of females but the observations are sometimes quite at variance with the ratio of female to male deaths recorded in the local returns of deaths. Whilst complete reliance cannot be placed on this use of the crude mortality statistics (*cf.* Joslin and Lombard

TABLE 2. THE SEX INCIDENCE OF DIABETES AT CERTAIN DIABETIC CLINICS

Author	Locality	Cases seen at clinic		Local deaths from diabetes
		Total number	Female to male ratio	Female to male ratio*
American:				
Altschul and Nathan (5)	Harlem, N.Y.	639†	4.0 :1	3.04:1† (New York, 1937)
		106‡	1.8 :1	2.09:1‡ (New York, 1937)
John (6, 7)	Cleveland 1921–27	1986	1.14:1	1.42:1 (Ohio, 1921–27)
Joslin (1)	Boston			
(i)	1898–1933	9853	1.13:1	1.54:1 (Massachusetts, 1901–32)
(ii)	1936–38	2887	1.28:1	1.92:1 (Massachusetts, 1933–38)
Wendt and Peck (8)	Detroit 1919–29	1073	1.83:1	1.36:1 (Michigan, 1919–29)
Wilder and Browne (9)	Mayo Clinic			
(i)	1924–28	1889	0.87:1	1.31:1 (Minnesota, 1924–28)
(ii)	1935–37	1998	0.77:1	1.50:1 (Minnesota, 1935–37)
British:				
Cammidge (10)	London	1000	0.67:1	1.42:1 (London, 1925)
Murray Lyon (11)	Edinburgh 1924–32 (approx.)	1700	1.82:1	1.84:1 (Scotland, 1924–32)
Present authors	Glasgow 1932–42	1309	2.26:1	2.06:1 (Scotland, 1931–40)

* Not adjusted for distortion of ratio in the process of certifying and recording deaths.
† Negro cases.
‡ White cases.

(4)), these comparisons do suggest that some clinics are not representative of the local diabetic population.

d) *The frequency of undiagnosed diabetes in the population of Scotland.* It should be pointed out that we have shown our diabetics to be representative only of *diagnosed* diabetes in the population of Scotland. It is quite probable that the type of diabetic in whom the disease goes undiagnosed is different from the average case of diabetes. Undiagnosed cases will tend to be mild and without definite symptoms. Furthermore, there is no reason to believe that lack of symptoms will affect male and female diabetics to the same extent. For example, genital pruritus was the chief complaint in 26 per cent of our female cases but in only 0.8 per cent of our male cases; it is conceivable that a number of these females would not have come for

diagnosis, were it not for the pruritus. It would therefore seem important to estimate the extent to which diabetes goes undiagnosed at different ages in the Scottish population.

In the case of young adults, a direct approach to the problem of the true number of diabetics in the population is possible through the use of data accumulated at the examination of army recruits. We have therefore obtained an analysis of the medical records of 413,110 consecutive male and female Scottish recruits. The ages covered were 17–45 years for men and

TABLE 3. DIABETES IN SCOTTISH ARMY RECRUITS

	Males	Females
Number of recruits examined	342,091	71,019
Average age (years)	27.1	21.7
Range (years)	17– 45	17–35
Diabetics found	594	26
Diabetics per thousand examined	1.74	0.37
American National Health Survey rate, in population of similar age composition (diabetics per thousand)	1.0	0.7
χ^2 test for diabetics found compared with number expected on the basis of the American National Health Survey	48.15*	7.58*

* The number found differs significantly from the number expected.

17–35 years for women and the only classes of the population exempted from military service were persons working in essential industries and women with young families. When glycosuria was found in the routine testing of urine, the test was repeated on the following day; if sugar were still present, the recruit was sent to a specialist for a glucose tolerance test and clinical assessment. The difficulties and decisions of the specialist are well illustrated by the paper of Peel and Peel (12) on diabetes among Scottish army recruits, but the important feature of the data which we have obtained is that it rests ultimately on clinical judgment of each individual case.

The incidence of diabetes in Scottish recruits is shown in Table 3. In order to compare this incidence with frequency of diabetes diagnosed in the ordinary course of events, we used the corresponding age groups of the American National Health Survey of chronic disease in the United States [quoted by Joslin (1)]. This abstraction of a portion of the American survey seems justified, since the over-all rate of 3.7 known diabetics per thousand of the population found by that survey agrees fairly well with our own

TABLE 4. AGE AND SEX INCIDENCE OF DIABETIC CASES

Age at onset	Diabetics seen at hospital		Population of Glasgow (1931 census)		Diabetic patients seen per 100,000 of Glasgow population	
	Males	Females	Males	Females	Males	Females
yrs.						
0–10	5	3	113,268	112,066	4	3
11–15	11	12	45,696	45,690	24	26
16–20	25	24	48,248	52,539	52	46
21–25	21	10	46,213	51,505	45	19
26–30	28	33	43,012	47,485	65	69
31–35	36	35	36,457	43,232	99	81
36–40	25	44	34,466	39,701	73	111
41–45	35	80	31,454	35,611	111	225
46–50	29	130	30,641	33,169	95	392
51–55	55	174	28,317	29,342	194	593
56–60	49	137	25,106	24,590	195	557
61–65	40	120	18,323	18,425	218	651
66–70	18	51	11,978	13,823	150	369
71–75	8	24	6,999	9,531	114	252
76–80	4	2	3,047	4,700	131	43
81–85	1	1	980	1,854	102	54
Unclassified	12	27	—	—	—	—
Up to 40	151*	161*	367,360	392,218	41.1	41.0
41 up	239*	719*	156,845	171,045	152	420
Unclassified	12	27	—	—	—	—
Total	402	907	—	—	—	—

* $\chi^2 = 60.82$; P = <0.01 (highly significant).

estimate[3] of 3.9 per thousand in Scotland. Table 3 indicates that diabetes was more frequent in the male Scottish recruits than in the corresponding age groups of the American survey; on the other hand female recruits showed a lower incidence than was found by the American survey. This low incidence in female recruits is not likely to be explained by the infrequency of married women among them, for it will later be shown that marriage is not a factor in the incidence of diabetes until after the age of 35.

[3] The total number of diabetics in Scotland was estimated by multiplying the true annual number of deaths from diabetes (Table 1) by the average duration of the disease computed for our clinic cases according to the expectations of life given by Joslin (1), *i.e.*, 1163 deaths by an average duration of 16.7 years, giving a total of 19,420 diabetics alive in Scotland, or 3.9 per thousand of the 1938 population.

It is therefore disturbing to find that Scottish recruits show a totally different incidence of diabetes in the sexes at an age when clinical experience shows a similar frequency in men and women (Table 4).

Numerically, young adult diabetics are an unimportant group. In middle life, diabetes is much more common but we have unfortunately no data to offer on the frequency of undiagnosed diabetes at this age. In view of this we must insist that our data are valid only in respect of the known diabetic population of Scotland.

e) *Control population.* For several of our observations a control population was used. This consisted of a random sample of hospital visitors, who were therefore of approximately the same social class as our diabetics.

TABLE 5. DEATH RATE FROM DIABETES ACCORDING TO AGE AT DEATH (CALCULATED FROM THE ANNUAL RETURNS OF THE REGISTRAR-GENERAL FOR SCOTLAND)

Age at death Yrs.	Average Annual Death Rate* for 1931–1940		
	Males	Females	Female/male ratio
0–	8.1	8.3	1.02:1
15–	30	24	0.80:1
35–	72	102	1.42:1
55 upwards	482	955	1.98:1

* Number of deaths per million of the population of similar age and sex.

Known diabetics were excluded from this group. In the section on heredity, nondiabetic patients were included in the control group.

SEX AND AGE INCIDENCE OF DIABETES

More women than men came to our clinic, the ratio being 2.26 females to every one male. This is in agreement with recent statistics from the United States and from most European countries (1).

The onset of symptoms was taken to represent the onset of the disease. In most of our cases diabetes started after the age of 40 (Table 4), the average age at onset being 45.1 years for men and 50.6 years for women. The tendency for diabetes to occur in middle life is actually greater than these figures would suggest, for the population after the age of 40 dwindles rapidly. In order to correct for this we have considered also the number of diabetics seen by us per 100,000 of the population of Glasgow of similar age and sex (Table 4). These adjusted figures (which must not be taken as absolute rates for diabetes in the population of Glasgow) show that up to the age of 40 both sexes are equally subject to diabetes; after this age

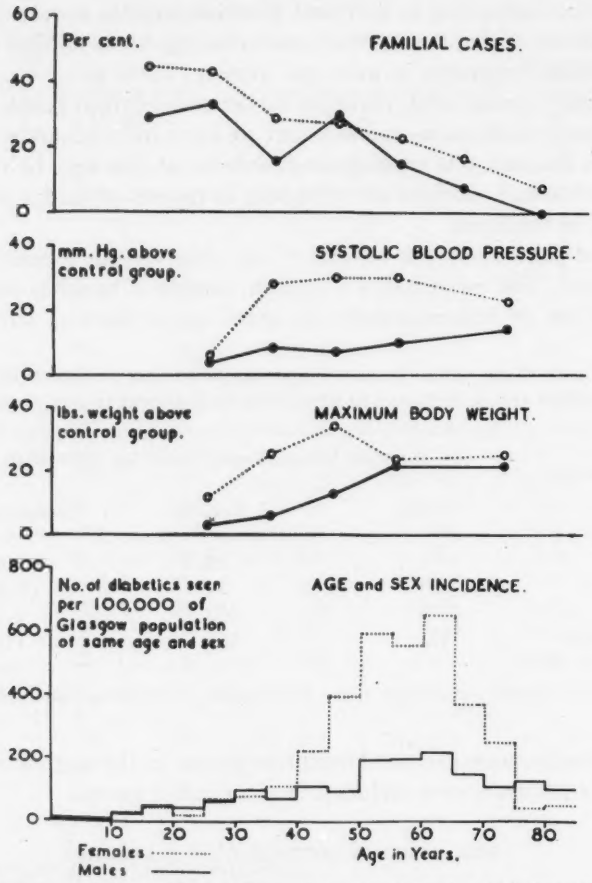

FIG. 2. Age and sex incidence, overweight, hypertension and frequeney of familial cases among Scottish diabetics.

its frequency in women increases rapidly while in men the increase does not become obvious until the age of 50 and is much less dramatic (Table 4 and Fig. 2). This finding is supported by the number of deaths from diabetes per million of the Scottish population at different ages (Table 5). During 1931–40, deaths from diabetes in Scotland were slightly more frequent in males up to the age of 34, but after this age more women than men died of diabetes.

THE INCIDENCE OF DIABETES IN MARRIED AND UNMARRIED WOMEN

When the proportion of married and unmarried women at our clinic was compared with the proportion present at similar ages in the general popu-

lation of Glasgow, it was found that married women formed an unduly high proportion of the diabetics from the age of 35 onwards (Table 6). When our cases of diabetes were considered per 100,000 of the population of Glasgow (Fig. 3), the disease was found to occur with the same fre-

TABLE 6. PROPORTIONS OF MARRIED AND UNMARRIED WOMEN DIABETES SEEN AT OUR CLINIC, COMPARED WITH THE PROPORTIONS OF MARRIED AND UNMARRIED WOMEN IN THE GENERAL POPULATION OF GLASGOW (1931 CENSUS)

Age group*	No. in group	Married	Unmarried	χ^2 test
25–34 years:		%	%	
Diabetics	59	64	36	0.54‡
General population	92,610	60	40	
35–44 years:				
Diabetics	109	85	15	3.53‡
General population	76,391	78	22	
45 years upwards:				
Diabetics	653	93.0	7.0	47.90†
General population	143,256	82.7	17.3	

* For diabetics, age and marital status at time of onset of diabetes.
† Statistically significant difference between groups.
‡ No statistically significant difference.

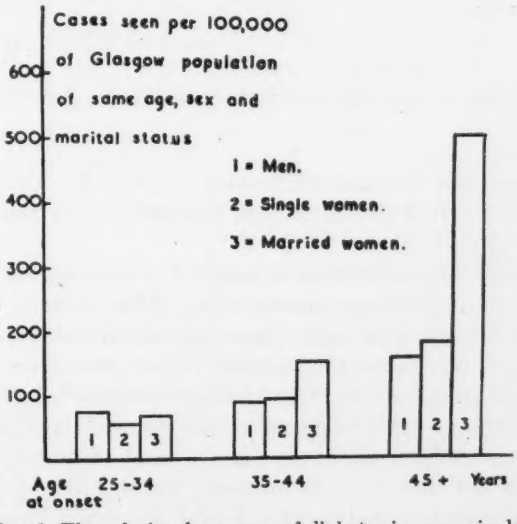

FIG. 3. The relative frequency of diabetes in men, single women and married women.

quency in men and in unmarried women, but to be rather more common in married women between 35 and 44 years of age, and much more common in married women after this age. Thus the higher incidence of diabetes in women as compared with men is due to a factor or factors associated with marriage. This conclusion is supported by recent mortality statistics from North America, where the death rate from diabetes per 100,000 of the population is much the same for men and unmarried women, but is

TABLE 7. DIABETIC SUBJECTS AND HOSPITAL VISITORS DISTRIBUTED ACCORDING TO SIZE OF FAMILY. DATA FROM MARRIED WOMEN 45 YEARS OF AGE OR OLDER AT TIME OF ONSET OF DIABETES OR, IN THE CASE OF CONTROL POPULATION, AT TIME OF QUESTIONING

	Diabetics		Controls	
	No. in group	Percentage of all subjects	No. in group	Percentage of all subjects
Total number of married women questioned	328	—	147	—
Those with:				
0–3 children	121	37	87	59
4–6 children	101	31	38	26
7 or more children	106	32	22	15
χ^2 test	23.71*			

* The distribution of the diabetic subjects is significantly different from that of the control subjects.

considerably greater for married women (1, 13, 14). A difference in the death rates for married and unmarried women has also been noted in England and Wales (15).

The high incidence of diabetes in married women appears to be related, at least in part, to previous childbearing. When women who developed diabetes after the age of 44 were compared with hospital visitors of similar age (Table 7), it was found that a much higher proportion of the diabetic women had had large families. This finding indicates that women with large families are specially liable to develop diabetes. Marriage and childbearing did not, however, affect the mean age at onset of diabetes in the group (Table 8), nor did they seem to influence the severity of the disease: the proportion of women diabetics who showed ketonuria (more than a trace by Rothera's test at any one visit to the clinic) and the proportion who

TABLE 8. AGE AT ONSET AND SEVERITY OF DIABETES IN RELATION TO MARRIAGE AND PREVIOUS CHILDBEARING. DATA FROM WOMEN 45 YEARS OR OLDER AT TIME OF ONSET OF DIABETES

Group of Women	No. in Group	Mean Age at Onset	Severity of Diabetes	
			Patients showing ketonuria	Patients taking insulin
		yrs.	%	%
Unmarried	32	57.8 ±1.46	16	50
Married:				
No children	37	56.9 ±1.31	11	38
1–3 children	84	54.4 ±0.60	8	40
4–6 children	101	55.8 ±0.61	11	38
7 or more children	106	56.6 ±0.50	6	48
χ^2 test	—	—	3.72*	3.56*

* The percentages do not differ significantly.

required insulin for stabilization did not change significantly with marital status or with the number of previous pregnancies (Table 8).

TABLE 9. HEIGHTS (WITH SHOES) OF AN ADULT DIABETIC POPULATION AND AN ADULT CONTROL POPULATION

Group	Diabetics		Controls		Difference	"t" test
	No. in group	Mean height	No. in group	Mean height		
		in.		in.	in.	
21–40 years:†						
Males	17	67.91 ±0.69	43	66.94 ±0.40	+0.97	1.22*
Females	11	64.16 ±0.81	98	63.14 ±0.27	+1.02	1.20*
41 years up:†						
Males	28	66.58 ±0.52	86	66.21 ±0.37	+0.37	0.52*
Females	68	61.82 ±0.35	112	62.73 ±0.23	−0.91	2.26§

* Difference not statistically significant.

† Age at onset for diabetics; age at time of examination for control population.

§ Difference statistically significant.

HEIGHTS AND WEIGHTS OF ADULT DIABETICS

Heights. The heights of some of our adult diabetics were known and were compared with the heights of visitors to the hospital. Table 9 shows

TABLE 10. BODY WEIGHTS OF A DIABETIC AND A NORMAL ADULT POPULATION. WEIGHTS RECORDED ARE SUBJECT'S ESTIMATED HEAVIEST AND INCLUDE CLOTHING

Age Group*	Diabetics		Controls		Difference	"t" test
	No. in group	Mean body weight	No. in group	Mean body weight		
	years	lbs.		lbs.	lbs.	
Males:						
21–30	30	148.1 ±4.16	16	145.7 ±4.90	+ 2.4	0.34†
31–40	40	156.4 ±3.79	42	150.4 ±3.08	+ 6.0	1.21†
41–50	47	172.2 ±4.03	46	159.4 ±4.13	+12.8	2.19§
51–60	64	177.5 ±3.94	35	156.7 ±3.99	+20.8	3.39§
61 upwards	32	188.3 ±5.63	32	166.8 ±5.45	+21.5	2.69§
Females:						
21–30	23	128.1 ±4.15	32	116.7 ±2.53	+11.4	2.42§
31–40	49	161.7 ±4.71	67	136.1 ±2.71	+25.6	4.95§
41–50	159	180.4 ±3.04	60	146.6 ±3.64	+33.8	6.20§
51–60	206	178.7 ±2.17	41	155.4 ±3.25	+23.3	4.57§
61 upwards	96	177.6 ±3.49	33	152.2 ±4.01	+25.4	3.93§

* Age at onset for diabetics; age at time of examination for control population.
† Not statistically significant.
§ Difference statistically significant.

that the diabetics were not significantly taller than the control population,[4] a finding which is in agreement with the observations of Joslin, Dublin and Marks (16) and of Blotner, Hyde and Kingsley (2) for adult diabetics. In contrast, diabetes in childhood tends to occur in tall children (White, in Joslin (1)). Our juvenile cases are too few to make our data worth quoting.

Weights. Diabetic patients and control subjects were asked to state what their maximum weights had been and it was found that women diabetics were significantly heavier than the control population from the age of 20

[4] Women acquiring diabetes after the age of 40 were significantly shorter than the corresponding control group (Table 9). This is due to the large number of multiparous women found among diabetics of this age. In both the diabetic and the control group we noted that women with large families tended to be of small stature, presumably because they originate mainly from the poorer classes of the community.

onwards, whereas the male diabetics were heavier from the age of 40 onwards (Table 10 and Fig. 2). Many authors have remarked that adult diabetics frequently give a history of previous obesity, and Joslin, Dublin and Marks (17) have demonstrated convincingly that a high incidence of diabetes occurs in occupations which favour obesity. Moreover, it has been shown that reduction in body weight may restore the sugar tolerance of obese diabetics (18), especially if the patients are treated early (19). These observations suggest that obesity not only precedes diabetes, but also plays a part in the production and maintenance of the diabetic state.

Does obesity account for the greater susceptibility of married women to diabetes? In Table 11 are shown our data for women diabetics and women

TABLE 11. MAXIMUM BODY WEIGHT IN RELATION TO MARRIAGE AND PREVIOUS CHILDBEARING. DATA FROM WOMEN 45 YEARS OR OLDER AT TIME OF ONSET OF DIABETES, OR, IN THE CASE OF THE CONTROL POPULATION OF HOSPITAL VISITORS, AT TIME OF QUESTIONING

Group of Women	No. in Group		Maximum Body Weight Lbs.			
	Diabetics	Controls	Diabetics	Controls	Difference	"t" test
Unmarried	32	26	153.8 ± 5.1	136.5 ± 4.0	+17.3	2.54*
Married:						
No children	35	13	166.0 ± 5.1	144.6 ± 7.2	+21.4	2.26*
1–3 children	82	73	172.3 ± 4.0	146.6 ± 3.0	+25.7	5.03*
4–6 children	106	38	185.8 ± 3.8	159.1 ± 4.1	+26.8	3.93*
7 or more children	97	21	186.5 ± 3.1	159.1 ± 4.6	+27.4	3.98*

* Difference statistically significant.

controls arranged according to marital status and number of children. In both the diabetic and the control group, married women were heavier than single women, and women with large families reached the greatest average weight. If we accept the evidence that obesity can be a factor in the production of diabetes, the greater frequency of obesity in married women provides one likely explanation for their higher susceptibility to diabetes. This subject has also been examined by Joslin (20). He studied women with onset of diabetes after the age of 45 and found that married diabetics had an average weight of 181 pounds, whereas unmarried diabetic women had an average weight of 161 pounds. He did not, however, find any difference between the average weights of childless and fertile married women with diabetes, but it should be noted that Joslin's clinic may not be a representative sample of diabetics (Table 2).

BLOOD PRESSURE IN DIABETES

It was our intention to record blood pressure readings as soon after the commencement of symptoms of diabetes as possible. For this reason, we include in Table 12 only the data obtained from patients who had had symptoms for less than one year before the date of examination. It was subsequently found that the blood pressure readings taken in all new cases seen at the clinic gave results almost identical with those shown in Table

TABLE 12. BLOOD PRESSURES OF A DIABETIC AND A NORMAL ADULT POPULATION (INCLUDES ONLY CASES SEEN WITHIN ONE YEAR OF THE ONSET OF SYMPTOMS)

Age group*	Diabetics		Controls		Difference	"t" test
	No. in group	Mean systolic blood pressure	No. in group	Mean systolic blood pressure		
years		mm. Hg		mm. Hg	mm. Hg	
Males:						
21–30	19	126.8 ± 4.31	11	122.7 ± 4.47	+ 4.1	0.60†
31–40	16	136.3 ± 6.40	28	128.2 ± 2.58	+ 8.1	1.34†
41–50	23	136.1 ± 4.36	35	129.4 ± 3.13	+ 6.7	1.26†
51–60	42	153.6 ± 3.83	22	143.6 ± 5.70	+10.0	1.44†
61 upwards	31	165.8 ± 4.95	16	151.9 ± 5.81	+13.9	1.69†
Females:						
21–30	8	123.8 ± 4.66	29	117.6 ± 2.37	+ 6.2	1.17†
31–40	23	146.1 ± 6.89	64	117.9 ± 1.93	+28.2	5.32§
41–50	70	162.3 ± 3.17	58	132.6 ± 2.75	+29.7	6.87§
51–60	114	176.3 ± 2.80	36	146.7 ± 4.53	+29.6	5.25§
61 upwards	85	181.5 ± 3.37	27	158.9 ± 5.72	+22.6	3.29§

* Age at onset for diabetics; age at time of examination for control population.
† Difference not statistically significant.
§ Difference statistically significant.

12 and we have used these more extensive data in all later tables relating to blood pressure.

Each diabetic's blood pressure was taken at the first visit to the clinic; after the patient had been lying on a couch for 15 to 30 minutes, readings were taken with the patient still in the recumbent position. It was impracticable to take the blood pressures of the control group (hospital visitors) under the same conditions; these subjects were examined seated, by the two observers who had taken most of the readings on the diabetics (Table 12 and Fig. 2). In view of the somewhat different conditions under which

the control population had to be examined, it was decided to retake the blood pressure readings of 250 diabetics who had attended the clinic for not more than five years. These readings were taken, with the patients seated, by a single observer who also studied a control group under similar conditions. This second group of data differ from those given in Table 12 in only one respect, *viz.* that the mean pressure of women diabetics between the ages of 40 and 60 years is slightly lower than the figures given in the table. As this does not affect the significance of the data given in the table we shall not give details about this second examination of patients and controls.

Table 12 shows that the mean systolic pressure of the female diabetics is significantly higher than that of the female control group from the age of 30 onwards. Blood pressure also tends to be high in males developing diabetes late in life, but the mean pressure of these cases is not significantly different from that of the control series. Somewhat similar observations were made by Major (21), who compared diabetics (duration of disease unstated) with a control group composed of hospital visitors and hospital staff. He found that the average blood pressure of the diabetics was significantly greater than that of the controls from the age of 50 onwards, and inspection of his data suggests that this was due to hypertension among the women diabetics only. However, Strauss (22) and Brull and Decharneux (23) compared diabetic and nondiabetic hospital cases and found that hypertension was more common in diabetics of both sexes. Blotner, Hyde and Kingsley (2) state that 7 per cent of male diabetic army recruits had hypertension, as compared with 2 per cent among nondiabetic recruits. Although statistical analysis shows this difference in incidence to be significant, it probably can be accounted for by the fact that the recruits with diabetes were older than the nondiabetic recruits. Wollaeger (quoted by Wilder (24)) states that the blood pressure of diabetics is not raised, but his control group consisted of patients attending the Mayo Clinic on account of headaches.

Hypertension and obesity. Obesity by itself causes a small increment in the blood pressure of healthy subjects (25, 26) and it has been claimed by Brull and Decharneux (23) that the unusual frequency of hypertension in diabetics is linked with their obesity. In analyzing their data, however, Brull and Decharneux did not consider male and female cases separately and it is possible that the apparent association between obesity and hypertension shown by their data was due to the fact that both of these conditions are specially frequent in diabetic women. Our own observations on this point are confined to women diabetics over 40 years of age at the time of examination. Using standard tables of weight, cases were arranged according to degree of obesity at the time of examination (Table 13). Two

TABLE 13. THE BLOOD PRESSURE OF WOMEN DIABETICS CONSIDERED IN RELATION TO BODY WEIGHT. NO ACCOUNT HAS BEEN TAKEN OF THE DURATION OF THE DISEASE

Group	Age*					
	41 to 50 years		51 to 60 years		61 years upwards	
	No. in group	Mean systolic blood pressure	No. in group	Mean systolic blood pressure	No. in group	Mean systolic blood pressure
		mm. Hg		mm. Hg		mm. Hg
Control group	58	132.6±2.75	36	146.7±4.53	27	158.9±5.72
Diabetic group:						
Underweight*	13	143.8±6.18	56	165.6±3.81	55	191.8±4.13
Up to 24% overweight*	21	174.5±6.03	80	183.2±3.51	33	182.2±4.80
25% or more overweight*	27	171.9±5.08	53	184.6±3.64	16	186.2±7.73

* At time of examination.

features of the data suggest that obesity does not play a large part in the hypertension of middle-aged diabetic women: a) patients who were underweight had a higher average blood pressure than the control group, especially in the later age groups; b) patients who were more than 25 per cent overweight had the same average blood pressure as patients who were less than 25 per cent overweight.

Hypertension and childbearing. We were unable to relate the hypertension of women diabetics to previous childbearing. When diabetic and control subjects were arranged according to size of family, it was found that those without children had the same average pressure as those with large families (Table 14). Our data also suggest that hypertension is not one of the factors

TABLE 14. BLOOD PRESSURE IN RELATION TO MARRIAGE AND PREVIOUS CHILDBEARING. DATA FROM WOMEN 45 YEARS OR OLDER AT TIME OF ONSET OF DIABETES OR, IN THE CASE OF THE CONTROL POPULATION, AT TIME OF EXAMINATION. BLOOD PRESSURE READINGS TAKEN AT PATIENT'S FIRST VISIT TO THE CLINIC

Group of Women	Diabetics		Controls	
	No. in group	Mean systolic blood pressure	No. in group	Mean systolic blood pressure
		mm. Hg		mm. Hg
Unmarried	22	168.2±5.1	13	145.4±9.4
Married:				
No children	34	177.4±5.5		
1–3 children	84	171.0±2.9	28	143.2±4.3
4–6 children	100	174.3±2.8	28	142.9±4.7
7 or more children	106	175.1±3.0		

There are no significant differences between the different groups of diabetics or between the different groups of control subjects.

causing diabetes to occur more frequently in women than in men. The specially high incidence of diabetes in middle-aged women is confined to married women, and if this were partly due to hypertension, one would expect to find a larger proportion of hypertensive cases and therefore a higher average blood pressure among married than among unmarried diabetic women. Table 14 shows that the mean blood pressure is the same for married and unmarried diabetic women.

THE HEREDITARY FACTOR IN DIABETES

The terms "familial" and "nonfamilial," as used in this paper, refer to whether or not a family history of diabetes was obtainable. Of 923 diabetics questioned, 23.2 per cent were found to be familial cases (Table 15). On re-

TABLE 15. INCIDENCE OF FAMILIAL CASES OF DIABETES

Age at onset of diabetes	Total number of cases	Those known to have diabetic relatives		
		Total number	Per cent of cases	χ^2 test
Males:				
Up to 40 years	108	26	24	2.29†
41 years upwards	168	28	17	
Females:				
Up to 40 years	104	37	36	7.83*
41 years upwards	543	123	23	

* The percentages are significantly different.
† The percentages do not differ significantly.

questioning 213 of them after they had been diabetic for more than five years, the figure obtained was 24.9 per cent, essentially the same proportion as previously ($\chi^2 = 0.28$; $P = 0.7 - 0.5$). These figures agree with most other estimates of the frequency of known familial cases among adult diabetics. A group of 2043 nondiabetic patients and hospital visitors was also investigated; only 5.3 per cent of these had family histories of diabetes. This is significantly less than the incidence among the diabetics ($\chi^2 = 208.8$; $P = <0.01$).

Thus a history of diabetes in the family can be elicited in only some cases. The proportion is highest when the disease begins early in life and is lowest when it starts late in life (Fig. 2). This observation is supported by the findings of Cammidge (27) and of Rudy and Keeler (28), but not by those of Joslin, Dublin and Marks (29). We shall now consider whether

this decline in the proportion of familial cases as age at onset advances can be related to any of the clinical features of diabetes.

a) Severity. It is generally conceded that diabetes in the young tends to be more severe than diabetes starting later in life. The decline in severity

TABLE 16. BODY WEIGHT PRIOR TO THE ONSET OF DIABETES, BLOOD PRESSURE AT THE TIME OF THE FIRST VISIT TO THE CLINIC, AND SEVERITY OF THE DISEASE IN DIABETICS WITH AND WITHOUT A FAMILY HISTORY OF DIABETES

Age at onset	Body weight		Blood pressure		Severity of diabetes			
	No. in group	Mean weight	No. in group	Mean systolic blood pressure	No. in group	Mean daily carbohydrate intake	Patients showing ketonuria	Patients taking insulin
		lbs.		mm. Hg		Gm.	%	%
16–40 years:								
Males:								
Familial	18	146±5.7	20	132±2.7	26	142	42	81
Nonfamilial	60	151±3.4	59	128±2.3	78	144	39	74
Females:								
Familial	28	145±7.8	33	144±5.4	35	119	37	89
Nonfamilial	56	148±3.9	66	142±3.5	72	111	44	75
41 years upwards:								
Males:								
Familial	27	176±6.4	29	159±6.0	28	130	21	57
Nonfamilial	116	179±3.0	141	153±2.2	144	133	18	56
Females:								
Familial	95	183±4.5	129	171±2.7	124	112	17	47
Nonfamilial	366	178±1.7	459	174±1.4	427	110	14	47

(The data for familial and nonfamilial diabetics of similar age and sex do not differ significantly in any of the above groups.)

coincides with the fall in the frequency of familial cases, and it might be suspected that the mild cases of diabetes seen in elderly people were "nonfamilial." However, when patients of comparable age were divided into familial and nonfamilial cases, it was found that the same proportion in each group required insulin for stabilization and that the same proportion in each group had ketonuria (Table 16). Thus there is no reason to suspect that nonfamilial diabetics are milder than cases known to have a family history of the disease.

b) Obesity and hypertension. Obesity is common among adult diabetics and hypertension is frequent in middle-aged diabetic women (Fig. 2), and both might be considered as possible nonhereditary causes of diabetes. The relationship of obesity and hypertension to the hereditary factor was investigated in two ways. First, the diabetics were arranged into familial and nonfamilial groups, and it was found that both groups had the same aver-

age blood pressure and the same average weight (Table 16). Secondly, middle-aged diabetic women were grouped according to degree of obesity and according to blood pressure (Table 17); the percentage of familial cases was found to be essentially similar in the various groups. There is accordingly no reason to suspect that nonfamilial cases of diabetes occur with disproportionate frequency among obese or hypertensive subjects.

TABLE 17. THE FREQUENCY OF FAMILIAL CASES OF DIABETES CONSIDERED IN RELATION TO BODY WEIGHT AND IN RELATION TO BLOOD PRESSURE (DATA FROM WOMEN OVER 40 YEARS OF AGE AT TIME OF ONSET OF DIABETES)

Group of women	No. in group	Mean age at onset	Those with diabetic relatives
		yrs.	%
Maximum Body Weight:			
Underweight and up to 24% overweight	164	57.0	26.2
25% to 49% overweight	113	54.5	22.1
50% or more overweight	66	53.0	28.8
χ^2 test	—	—	1.10*
Systolic Blood Pressure:			
Up to 144 mm. Hg	95	52.8	22.1
145 to 194 mm. Hg	318	55.8	23.6
195 mm. Hg upwards	108	58.2	20.4
χ^2 test	—	—	0.50*

* The percentages do not differ significantly. The patients were also classified into 10-year age groups and then arranged according to body weight and according to blood pressure. The values of χ^2 so obtained did not reach significance in any one decade or in the aggregate of decades.

c) *Previous childbearing.* Family histories were investigated in women developing diabetes after the age of 44 years and in a control series of nondiabetic patients of similar age; both groups were arranged according to marital status and number of children (Table 18). In the diabetic group, a family history of the disease was less frequently obtained from women with large families than from those with small families. This is not due to differences in the mean ages of the various groups (Table 8): nor is it due to greater ignorance of the family history among women with large families, for in the control group family histories of diabetes were just as frequently obtained from women with large families as from the rest of the group (Table 18). It has therefore been concluded that some factor associated

with previous childbearing increases the frequency of nonfamilial cases of diabetes, resulting in a smaller proportion of familial cases among women with large families. Although such women have a greater maximum body weight than women with small families (Table 11), obesity is not the reason for the larger proportion of nonfamilial cases of diabetes among fertile women, for previous childbearing was found to affect the proportion of

TABLE 18. THE FAMILIAL FACTOR IN RELATION TO MARRIAGE AND PREVIOUS CHILDBEARING (DATA FROM WOMEN 45 YEARS OF AGE OR OLDER AT TIME OF ONSET OF DIABETES OR, IN THE CASE OF NONDIABETIC PATIENTS, AT TIME OF QUESTIONING)

Group of women	Diabetic patients		Nondiabetic patients	
	No. in group	Those with diabetic relatives	No. in group	Those with diabetic relatives
		%		%
Unmarried	32	34.4	54	9.0
Married:				
No children	37	32.4	57	
1–3 children	84	27.4	200	8.5
4–6 children	101	21.8	131	8.4
7 or more children	106	17.9	88	10.2
χ^2 test	6.24*		—	

* Although the value of χ^2 for the series is not significant, there is a significant difference between the frequency of familial cases among all childless women (married as well as single) and the frequency among women with 7 or more children ($\chi^2 = 5.44$; $P = 0.02 - 0.01$).

familial cases among women having the same degree of obesity (Table 19). Thus obesity is not the only factor which increases the susceptibility of childbearing women to diabetes.

Sex linkage. Penrose and Watson (30) examined the relative frequency of diabetes in brothers and sisters and found that the disease had a definite tendency to recur in the same sex when more than one member of the sibship was affected. They concluded that some factor in the inheritance of diabetes was carried by the chromosomes determining sex. Among the families of our own cases, there were 14 pairs of diabetic brothers, 54 diabetic brother-sister pairs and 100 pairs of diabetic sisters. These data show a suggestive though not significant excess of like-sexed siblings ($\chi^2 = 2.79$; $P = 0.10 - 0.05$) which might be interpreted as supporting a sex-linked in-

herited factor in diabetes. The explanation of this excess of like-sexed siblings is, however, more likely to be provided by social rather than by genetic factors. During 1930–32, deaths occurring in England and Wales were classified according to social status (15) and in the case of diabetes it was found that the highest death rate in males was in the upper classes, whereas the highest death rate in females was in the lower classes. This

TABLE 19. FREQUENCY OF POSITIVE FAMILY HISTORIES RELATED TO SIZE OF FAMILY AMONG DIABETIC WOMEN OF VARIOUS WEIGHTS

Group I: Single women, and married women with up to 2 children.
Group II: Married women with 6 more children.
Data from women 45 years of age or older at time of onset of diabetes

Group of women	No. in group	Mean age at onset	Those known to have diabetic relatives	χ^2 test
		yrs.	%	
Underweight and up to 19% overweight:				
Group I	54	56.7	30	0.39†
Group II	34	60.6	24	
20 to 39% overweight:				
Group I	17	57.9	35	3.99*
Group II	46	56.2	13	
40% or more overweight:				
Group I	25	50.8	44	7.57*
Group II	38	55.9	13	

* The frequency of familial cases is significantly different in the two groups.
† The frequency of familial cases does not differ significantly in the two groups.

suggests that the sex incidence of diabetes is modified by social status, namely that men form a higher proportion of cases in the upper classes than they do in the lower classes. Since the members of a family tend to remain within the same social class, this means that the occurrence of diabetes in two brothers is favored in the upper classes and the occurrence of diabetes in two sisters in the lower classes. In a group of diabetics representative of all social classes one will therefore encounter pairs of diabetic brothers and pairs of diabetic sisters out of proportion to the number of diabetic brother-sister pairs found. This seems an adequate explanation for the small excess of like-sexed siblings with diabetes which our clinic provides.

Heredity and age at onset. When diabetes occurs in more than one member of the same sibship, it often starts in each at about the same age (30). Thus, on investigating 32 sib-pairs, we found a highly significant correlation coefficient (+0.668) for age at onset. Patients are, however, commonly questioned within a few years of the onset of the disease; in the case of young diabetics, this means that siblings developing diabetes late in life are omitted. The data are therefore biassed in favor of an association between ages at onset. In an attempt to eliminate this fallacy, we considered

TABLE 20. AGE AT ONSET OF DIABETES IN PAIRS OF SIBLINGS

(Only clinic cases with onset after the age of 49 years were investigated. In this table the age at onset of diabetes in their siblings (group A) is compared with the age of onset among familial cases in general (group B))

Age at onset Yrs.	Males		Females	
	Group A	Group B	Group A	Group B
	No. of cases	No. of cases	No. of cases	No. of cases
0–20	1	7	1	8
21–30	5	11	1	12
31–40	1	8	3	17
41–50	1	14	20	47
51–60	6	11	26	53
61 upwards	2	3	1	23
Up to 40 years	7	26	5	37
41 years upwards	9	28	47	123
χ^2 test (one degree of freedom)	0.10†		4.51*	

* The two groups differ significantly in age distribution.

† The two groups do not differ significantly in age distribution.

only the siblings of cases who developed the disease after the age of 49 years (Table 20). If the age at onset in siblings is related, then this group of elderly diabetics should rarely provide siblings who developed diabetes when young. Our data show (Table 20) that diabetes starting in brothers of these elderly patients conformed to the general age distribution of the disease in male familial cases, nearly half having had symptoms before the age of 41 years. On the other hand, sisters of these elderly patients provided fewer young diabetics than would be expected on a random distribution. This finding may not, however, be evidence of genetic influence over

the age at which diabetes starts. Other factors may influence both members of a sib-pair. Thus, previous childbearing appears to increase the susceptibility of women to diabetes after they have reached middle age (Table 7). In the lower classes, families are often large and sisters in this social grade might be expected on this account to have a special liability to develop diabetes in middle life. The elucidation of genetic influences on the age at which diabetes starts must accordingly await more comprehensive methods for analyzing the data.

ASSOCIATION OF DIABETES WITH OTHER ENDOCRINE DISEASES

About 2 to 3 per cent of patients with hyperthyroidism also suffer from diabetes (1, 31). Since the thyrotoxicosis occurs mainly in young adults (32) this would appear to be a much higher frequency of diabetes than would be expected by chance (*cf.* Table 3). It must therefore be concluded that the two conditions are related.

Of our 1309 diabetics, 13 (4 men and 9 women) had hyperthyroidism; 3 of these cases were diagnosed solely on clinical grounds but the remaining 10 had sufficiently detailed records to assure us that they conformed to the standards laid down by Joslin and Lahey (33) for the diagnosis of the two diseases in combination. This incidence of hyperthyroidism in diabetes (1.0 per cent) is of the same order as that recorded by most other authors (1, 33, 34, 35), though some estimates are slightly higher (31, 36, 37). According to Joslin (1) the thyrotoxicosis starts either before or at the same time as the diabetes in the majority of cases. If thyrotoxicosis was the only cause of diabetes in such cases, one might expect that the combination would be most common at the age when thyrotoxicosis is most frequent and that a family history of diabetes would be obtained as infrequently as from nondiabetic subjects. The data of Wallace (32) indicate that in Scotland the average age at onset of thyrotoxicosis alone is 30.5 years. Our clinical data show that the average age at which diabetes starts is 45.1 years for men and 50.6 years for women. It is therefore interesting to find that the average age at which diabetes started in our thyrotoxic cases of diabetes was 42 years for males and 43 years for females. Thus the age incidence of diabetes associated with hyperthyroidism is not notably different from that of diabetes alone, a finding which conforms with the observations of John (34) and of Joslin (1). Like Joslin and Lahey (33) and Foster and Lowrie (31), we found a family history of diabetes to be as common among the thyrotoxic cases as among other diabetics, but our cases are too few to carry much weight. The evidence is thus against thyrotoxicosis being the sole cause of diabetes in subjects suffering from both conditions.

Frank pituitary disease was seldom seen at our clinic. Two patients with acromegaly came for treatment of their diabetes and in one case of diabetes

pituitary basophilism was considered to be present. On the other hand, diabetes is well known to be a common sequel to acromegaly. Thus Coggeshall and Root (38) found 29 diabetics among 156 cases of acromegaly seen in Massachusetts. This is of course much too high an incidence of diabetes to occur by chance. A family history of diabetes was obtained from 21 per cent of the acromegalics with diabetes (*i.e.*, about as commonly as at Joslin's diabetic clinic in Massachusetts (29)) and from only 2 per cent of the acromegalics without diabetes. This suggests that, as in the case of thyrotoxicosis, acromegaly is not the only factor involved in the production of diabetes, when the two diseases occur together.

MISCELLANEOUS FACTORS IN THE ONSET OF DIABETES

The influence of infections on the onset of diabetes has been frequently discussed (see Marble, in Joslin (1)). Among our own patients, 6.5 per cent

TABLE 21. SEPSIS ASSOCIATED WITH THE ONSET OF DIABETES

Group I: Diabetic patients without sepsis (age at onset of diabetes)
Group II: Cases where sepsis was apparently associated with onset of diabetes (age at onset of diabetes)
Group III: Consecutive nondiabetic patients admitted to the sepsis wards (age on admission)

Group	No. in group	Mean age	Difference	"t" test
		yrs.	yrs.	
Males:				
Group I	364	44.75 ±0.87	5.75	1.70†
Group II	26	50.50 ±3.35		
Group III	312	34.49 ±1.12	16.10	3.98*
Females:				
Group I	826	50.93 ±0.45	1.22	0.67†
Group II	54	52.11 ±1.93		
Group III	249	31.55 ±1.02	20.56	8.69*

* Difference statistically significant.
† Difference not statistically significant.

of the males and 6.0 per cent of the females were first found to be diabetic when suffering from some septic condition, usually a boil or carbuncle. Table 21 shows that nondiabetic patients admitted to the hospital on account of septic conditions were frequently young people, whereas those in whom diabetes was also found to be present were mainly of middle age. This implies that, if infection does play a part in the onset of diabetes, it usually does so at the age when diabetes occurs most commonly and not at the age when sepsis is most frequent. Furthermore, of the 80 diabetics

in whom the onset of diabetes apparently coincided with a septic process, 18 per cent had a family history of diabetes. This figure does not differ significantly from the frequency of familial cases among other diabetics ($\chi^2 = 1.58$; $\rho = 0.3 - 0.2$).

In view of the recent experimental production of diabetes with alloxan (39), and its possible implications in purine metabolism, it should be added that no case of gout has been encountered at our diabetic clinic. Gout is a rare disease in Scotland, and its rarity appears to extend to the diabetic population.

DISCUSSION

From our investigation of Scottish diabetics and from an examination of the literature we have concluded that certain features (a history of diabetes in the family, obesity, hypertension, large families, thyrotoxicosis, acromegaly and perhaps sepsis) occur in combination with diabetes more frequently than they should by chance. Since these conditions are found early in the course of the disease, we must consider what part they play in the causation of diabetes.

In the first place, there is the hereditary factor. This can be established in only about a quarter of the cases but many authors assume that the other diabetics, though unable to trace a relative with diabetes, are also hereditary cases. Do any of our observations make this standpoint untenable? Our data show (Fig. 2) that, as age at onset increased, family histories of diabetes were less often obtained and this might be taken to indicate a growing number of nonhereditary cases of diabetes as age at onset advances. However, Joslin, Dublin and Marks (29) give several reasons for believing that such a change in the proportion of hereditary cases may be apparent rather than real. We have also considered whether there is any reason for believing that obesity, hypertension, childbearing, thyrotoxicosis, acromegaly and sepsis are nonhereditary causes of diabetes. If any one of them could act as such, one would expect the proportion of cases with a family history of diabetes to be unusually low among diabetics with that condition. The data show that a family history of diabetes occurred as commonly among diabetics suffering from obesity, hypertension, thyrotoxicosis, acromegaly or sepsis, as among diabetics who did not have these conditions. This indicates that, whatever may be the part played by these conditions in the causation of diabetes, they do not act as nonhereditary causes to any important extent. On the other hand, a significantly lower proportion of familial cases was observed among women diabetics with large families. Before accepting this as conclusive evidence that a nonhereditary form of diabetes occurs among fertile women, it is as well to consider whether there may be any alternative explanation. One such ex-

planation is that the inheritance of diabetes occurs through several genetic defects and that childbearing increases the susceptibility of the individual to inherited diabetogenic factors which do not often appear (low penetrance). A definite decision cannot be arrived at without further work, but we shall assume as a working hypothesis that cases of diabetes occurring among childbearing women are all based on an inherited defect.

In the second place, we must consider the part played in the etiology of diabetes by the factors other than heredity. Since none of these factors (with the possible exception of childbearing) appears to be a nonhereditary cause of diabetes, their relationship to diabetes may take one of three forms: i) that of a condition linked genetically to diabetes. Such a condition would be found in association with diabetes but would not increase susceptibility to diabetes. ii) that of a secondary (aggravating) factor which increases the susceptibility of persons predisposed to diabetes by inheritance. iii) that of an early result of diabetes. We shall consider each feature of the diabetic separately. a) Investigations already referred to (17, 18, 19) make it probable that obesity is a factor in the causation of diabetes and not merely genetically linked to it or occurring as an early stage in the course of the disease. b) From the age of 30 onwards, diabetic women were found to have a higher average blood pressure than a control population of hospital visitors (Table 12). It was concluded, however, that hypertension was not a significant factor in the causation of diabetes in this group of women. It is most likely to be an early result of diabetes. c) Previous childbearing can only fall into the category of a cause of diabetes. d) Evidence from animal experiments shows that thyroid administration can provoke diabetes under suitable conditions of pancreatic impairment (40). Thyrotoxicosis is therefore likely to increase susceptibility to diabetes. e) The existence of a diabetogenic factor in the anterior lobe of the pituitary gland is widely accepted and it is reasonable to assume that this gives acromegalic subjects an increased susceptibility to diabetes. f) The relationship of sepsis to the onset of diabetes is difficult to assess. The well-known effect of sepsis in aggravating the severity of established cases of diabetes indicates that its occurrence prior to the onset of diabetes might increase the individual's susceptibility to diabetes.

Considering these various etiologic factors together, we have tentatively divided them as follows:

A) A hereditary factor or factors, fundamental to virtually all cases.
B) Factors increasing the susceptibility of persons predisposed to diabetes by the hereditary factor or factors:
   i) Obesity.
   ii) One or more factors associated with childbearing.
   iii) Minor factors (thyrotoxicosis, acromegaly, ?sepsis).

There may well be other factors which increase susceptibility to diabetes. For example, several authors (3 and 41–45) have described a decline in sugar tolerance which occurs in both normal and obese members of the general population with advancing age. The factors responsible for this have apparently not been investigated.

SUMMARY

1. Certain features of a group of 1309 diabetics have been studied. The group was considered to be representative of Scottish diabetics since the sex distribution of cases corresponded to the sex distribution of deaths from diabetes recorded in the official mortality statistics for Scotland. Evidence is presented which justifies the use of Scottish mortality statistics for this purpose. A study of the incidence of diabetes in 413,110 Scottish recruits (male and female) suggested that in the general population the sex distribution of persons with undiagnosed diabetes might not be the same as that of persons known to have the disease.

2. In both sexes the disease started most frequently after the age of 40 years. The sex incidence was equal up to the age of 40; thereafter, female diabetics were much more common than male diabetics.

3. The high frequency of diabetes in women of middle age was confined to married women and appeared to be related, at least in part, to previous childbearing. The age at onset and the severity of the disease in this group of women were apparently uninfluenced by marriage and childbearing.

4. The adult diabetics were no taller than the control group (hospital visitors). In the case of women diabetics the maximum weight was significantly greater than that of the control population from the age of 20 onwards, and in the case of male diabetics from 40 onwards. In both diabetic and control groups, married women were heavier than single women.

5. The mean blood pressure was significantly higher in female diabetics after the age of 30 years than in the corresponding control group. This hypertension could not be adequately explained on the grounds of obesity; it was not related to previous childbearing.

6. Of 923 diabetics questioned, 23.2 per cent gave a family history of diabetes. As age at onset of the disease increased, positive family histories decreased. There was no relationship between the presence of a positive family history and the severity of the disease. The frequency of a positive family history in obese and hypertensive patients did not differ from that of the group of diabetics as a whole. In the group of middle-aged married women, those with the largest families gave the fewest positive family histories. It was considered that there was no proof of partial sex linkage of the hereditary factor, and no convincing evidence that the age at onset is determined by inherited factors.

7. Thyrotoxicosis was present in 1 per cent of the cases. The age at onset in these cases was similar to that in diabetes generally.

8. Sepsis was associated with the onset of diabetes in 6 per cent of cases, but the average age at onset was that for diabetes in general, and a family history of diabetes was obtained in 18 per cent of the cases.

9. After considering these data, it was concluded that the etiologic factors in human diabetes could be tentatively divided into

a) A hereditary factor or factors, fundamental to almost all cases.
b) Factors increasing the susceptibility of persons predisposed to diabetes by the hereditary factor:
   i) Obesity.
   ii) One or more factors associated with childbearing.
   iii) Minor factors (thyrotoxicosis, acromegaly, ?sepsis).

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EFFECT OF ROENTGENOTHERAPY ON URINARY 17-KETOSTEROID EXCRETION IN ANKYLOSING SPONDYLARTHRITIS*

ROLAND A. DAVISON M.D., PETER KOETS, Ph.D.,** AND WILLIAM C. KUZELL, M.D.†

From the Departments of Medicine, of Obstetrics and Gynecology, and of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, California

FEW studies of urinary 17-ketosteroid excretion have been made in rheumatic disease. Fraser and co-workers (1) found diminished excretion in a 16-year-old female with rheumatoid arthritis. Chou and Wang (2) reported low values in rheumatic fever. In 7 males with rheumatic disease, Forbes and associates (3) found the average excretion to be 7.5 mg. in 24 hours, with a range of 2.7 to 11.5 mg., and in females an average of 4.5 mg. with a range of 1.2 to 7.8 mg. Low excretion is found in malnutrition, anemia, hypothyroidism, panhypopituitarism, Addison's disease, and chronic debilitating diseases (1, 2, 3, 4, 5), whereas high excretion occurs in carcinoma of the adrenal cortex, hyperplasia of the adrenals, masculinizing ovarian tumors, hirsutism of females and in Cushing's syndrome (1, 6, 7).

Although ankylosing spondylarthritis is a chronic debilitating disease accompanied by malnutrition, anemia, and pronounced muscle wasting in its advanced stage, we have found increased urinary 17-ketosteroid excretion in all of 13 males having this disease (8). Our study of 17-ketosteroid excretion has been extended and the results are reported in this paper. Since roentgenotherapy exerts a pronounced beneficial effect on the course of the disease in these patients (9, 10, 11, 12), giving relief of symptoms, abatement of objective physical findings, and improved well being even in advanced cases, observations were made to determine the effects of roentgenotherapy on 17-ketosteroid excretion during the course of such treatment. The cases studied comprised 31 males and 4 females. The majority were patients in the outpatient clinic of Stanford University Medical School; a few were private patients. Five males and one female were Army personnel provided by Major Potter, all of whom were examined by one

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** Agnes Lemme Schilling Fellow in Obstetrics and Gynecology.

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TABLE 1.

Case	Sex	Age (yrs.)	Duration of symptoms, (yrs.)	Status of disease; chief symptoms and nutritional state of patient at time of initial estimation of 17-ketosteroid excretion	Sedimentation rate, mm./hr., Wintrobe	Joints affected, as shown in roentgenograms	Initial urinary 17-ketosteroids, mg./24 hrs.	Range of 17-ketosteroid values during treatment, mg./24 hrs.	Roentgen therapy	
									No. of courses	Total rhegmas*
1. W.P.	M	23	1	Mild. Pain and stiffness of lower back. Little disability.	24	Sacroiliacs.	21.5	20–46 (*see* Fig. 6)	2	2640
2. D.H.	M	28	1	Active, mild. Backache after standing.	5	Sacroiliacs.	29.5			
3. G.C.	M	19	3	Active, rapidly progressing. Diminished chest expansion. Nutrition good.	7	Sacroiliacs (ankylosis); lumbar apophyseal and thoracic.	16.5	6–22	2	1800
4. H.J.	M	21	⅙	Active, mild. Low back pain and stiffness, 2 mos. Moderate muscle spasm.	35	Sacroiliac and lumbar apophyseal.	34.0	19	1	675
5. M.K.	M	26	1	Active, mild. Early morning pain and stiffness. Lumbar flexion limited by muscle spasm.	20	Left sacroiliac, hazy.	15.0		3	2700
6. R.C.	M	30	1	Active, rapid progression in 6 mos. Low back pain and stiffness. Nutrition good.	47	Sacroiliacs, sclerotic. X-rays 6 mos. before showed little change.	18.5		3	
7. L.N.	M	22	1	Active, rapidly progressing. Much lumbar pain and stiffness and muscle spasm.	14	Sacroiliacs, blurred.	20.0	16–39.5 (*see* Fig. 5)		
8. L.K.	M	30	2	Inactive, mild. Stiffness of lower back. Previous gonorrhea.	10	Sacroiliacs, sclerotic.	39.0			
9. R.P.	M	25	1½	Active, rapidly progressing. Much pain in lumbar and dorsal spine with limitation of movement by muscle spasm. Febrile.	12	Sacroiliacs, hazy.	27.0	(*see* Figs. 2 and 3)	2	2400
10. E.G.	M	36	3	Active, mild. Pain and stiffness in neck and lower back. Associated hirsutism. Nutrition good.	16	Sacroiliacs.	36.0			
11. W.S.	M	40	2	Active, severe. Very stiff back and much pain.	44	Sacroiliacs.	24.0	9.2–14		
12. J.C.	M	25	3	Active, mild, rapidly progressing. Scoliosis and rigid lumbar spine. Nutrition good.	30	Right sacroiliac, hazy.	34.0	23–37	1	1200
13. C.C.	M	24	3	Active, rapidly progressing. Nutrition good.	32	Sacroiliacs, sclerosed.	40.0			
14. W.G.	M	39	4	Stiffness in lower back only. Nutrition good.	40	Sacroiliacs and lumbar, ankylosed.	28.5	22–47	3	4065
15. G.E.	M	33	4	Active, severe, rapidly progressing. Complete disability. Stiffness of spine and swelling of peripheral joints.	53	Sacroiliacs, moderately sclerosed; lumbar 1–2, calcified ligaments.	26.0	13.2–41.8	1	900
16. V.K.	M	28	4	Active, severe. Much disability. Dorsal kyphosis.	45	Sacroiliacs, lumbar, dorsal, and cervical. Entire spine ankylosed.	34.0	12.5–34	3	5150
17. R.K.	M	33	7	Severe pain and stiffness of hips and neck.	20	Sacroiliacs and lumbar, calcified ligaments.	30.0	30–42.5	1	2200
18. W.L.	M	30	6	Active, mild. Stiff lumbar and dorsal spine. Nutrition good.	28	Sacroiliacs, ankylosed.	19.0	17.5–24.5	2	3080

TABLE 1.—(*Continued*)

Case	Sex	Age (yrs.)	Duration of symptoms, (yrs.)	Status of disease; chief symptoms and nutritional state of patient at time of initial estimation of 17-ketosteroid excretion	Sedimentation rate, mm./hr., Wintrobe	Joints affected, as shown in roentgenograms	Initial urinary 17-ketosteroids, mg./24 hrs.	Range of 17-ketosteroid values during treatment, mg./24 hrs.	Roentgen therapy	
									No. of courses	Total rhegmas*
19. C.T.	M	38	10	Active, mild. Patient capable of mild activity. Stiffness of entire spine. Nutrition good.	12	Sacroiliacs, lumbar, and dorsal, ankylosed.	41.0			
20. W.H.	M	25	10	Active, severe. Much pain, stiffness of lumbar and dorsal spine and loss of strength. Nutrition poor.	12	Sacroiliacs (sclerosis and cystic changes); lumbar apophyseal, hazy.	19.0		1	1800
21. B.Y.	M	25	?	Active, mild. Stiff lumbar spine. Nutrition good.	12	Right sacroiliac; all lumbar.	22.5	18–22.5	2	1760
22. F.Y.	M	39	18	Little disability. Nutrition poor.	13	Sacroiliacs, ankylosed; right hip.	22.5	22.5–35	3	2800
23. C.B.	M	37	16	Advanced disease. Whole spine stiff. Nutrition good.	32	Sacroiliacs, lumbar, and dorsal; calcified ligaments.	43.5		1	600
24. F.F.	M	35	15	Entire spine stiff. Muscular weakness and fatigue. Nutrition poor.	25	Sacroiliacs to cervical, completely ankylosed.	25.0	6.2–25	1	1250
25. W.G.	M	32	13	Bedridden. Stiffness of entire spine. Emaciation and muscle atrophy.	15	Sacroiliacs, cervical, dorsal, and lumbar.	10.5	6–22.5 (*see* Fig. 4)		
26. M.M.	M	36	17	Active, severe. Completely stiff spine. Severe pain.	37	Sacroiliacs, lumbar, dorsal, and cervical; calcified ligaments.	23.5			
27. W.P.	M	43	26	Active, mild. Completely stiff spine.	35	Sacroiliacs, lumbar, dorsal, and cervical; calcified ligaments.	23.5			
28. B.P.	M	42	10+	Active.	26	Sacroiliacs, lumbar, dorsal, and cervical.	27.0	16.5–39	2	3500
29. R.S.	M	41	2(?)	Inactive, slight cervical pain. Entire spine stiff. Nutrition excellent.	8	Sacroiliacs, ankylosed; lumbar and dorsal, calcified ligaments.	31.0			
30. W.M.	M	30	7	Inactive. Stiff spine. No symptoms. Previous x-ray therapy.	20	Sacroiliac, lumbar, dorsal, and cervical.	22.5			
31. W.N.	M		3	Active, rapidly progressing.	26	None	26.0			
32. R.H.	F	25	6	Aching and stiffness of lower back.	45	Right sacroiliac, hazy.	19.5			
33. E.R.	F	39	14	Active, slowly progressing. Pain and tenderness of dorsal spine.	24	Sacroiliacs, sclerosed; lumbar 1–2, calcified ligaments.	40.0			
34. L.B.	F	41	18	Active, mild. Stiff neck and lower back.	30	Sacroiliac and cervical	23.0			
35. M.O.	F	32	7	Some back pain. Nutrition excellent. Infectious type of anemia. Previous x-ray therapy.	19	3–4–5 lumbar apophyseals, ankylosed.	16.0			

* Skin roentgens.

of us (R.D.). Four were Navy personnel whose records and roentgenograms were made available to us by Commander Cuttle.

The occupations of these patients were varied. The ages ranged from 19 to 43 years; duration of symptoms from less than one, to twenty-six years. Two of the patients (cases 30 and 35) had roentgenotherapy prior to our examination of them. The disease showed all grades of activity; in three patients it appeared to be relatively inactive; in the remainder, including

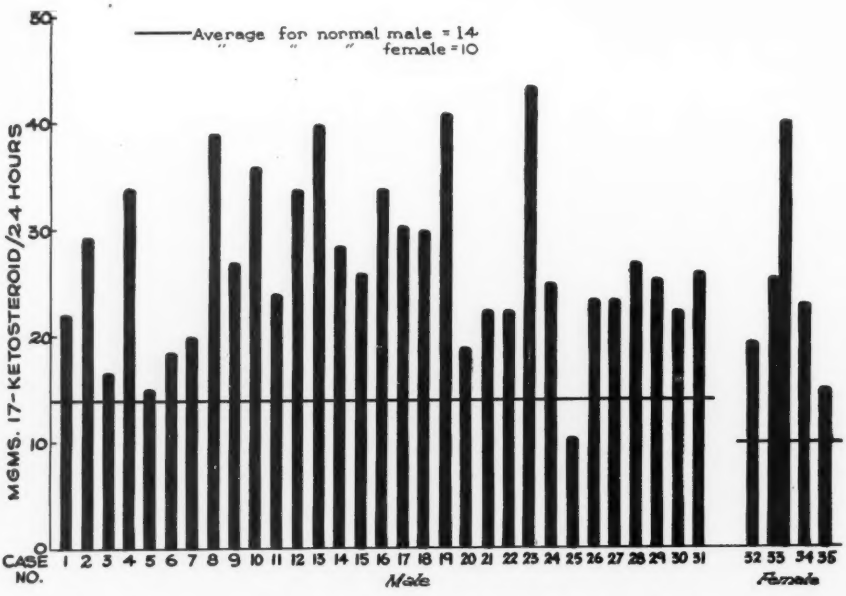

FIG. 1. Urinary excretion of 17-ketosteroids (mg.) in 24 hours in males and females with ankylosing spondylarthritis.

those with histories dating back many years, there was objective evidence of active disease. The nutritional state varied from excellent to poor. The clinical status of the individual patients is given in Table 1.

Roentgenograms were made of the sacroiliac joints and the entire spine in all patients. Roentgen ray findings (recorded in Table 1) indicated positive evidence of the usually accepted changes characteristic of this disease. The urinary 17-ketosteroid excretion in milligrams per 24 hours is given in Table 1 and presented graphically in Figures 1 to 6. The method of determining urinary 17-ketosteroids was adapted from that by Robbie and Gibson, and described in our preliminary report (8). The x-ray therapy consisted of 6 daily treatments in each course. The cervico-dorsal and lumbo-

sacral areas were treated on alternate days using the following factors: 200 KV; 20 milliamps; 70 cm. anode skin distance; 1.0 mm. copper, half-value layer; and 15×8 cm. area of the average field treated. These courses of therapy were repeated in one month and again in three months.

17-KETOSTEROID EXCRETION

The average urinary 17-ketosteroid excretion in 24 hours by normal males is 14 mg.; by females, approximately 10 mg. (2, 3, 13, 14). The av-

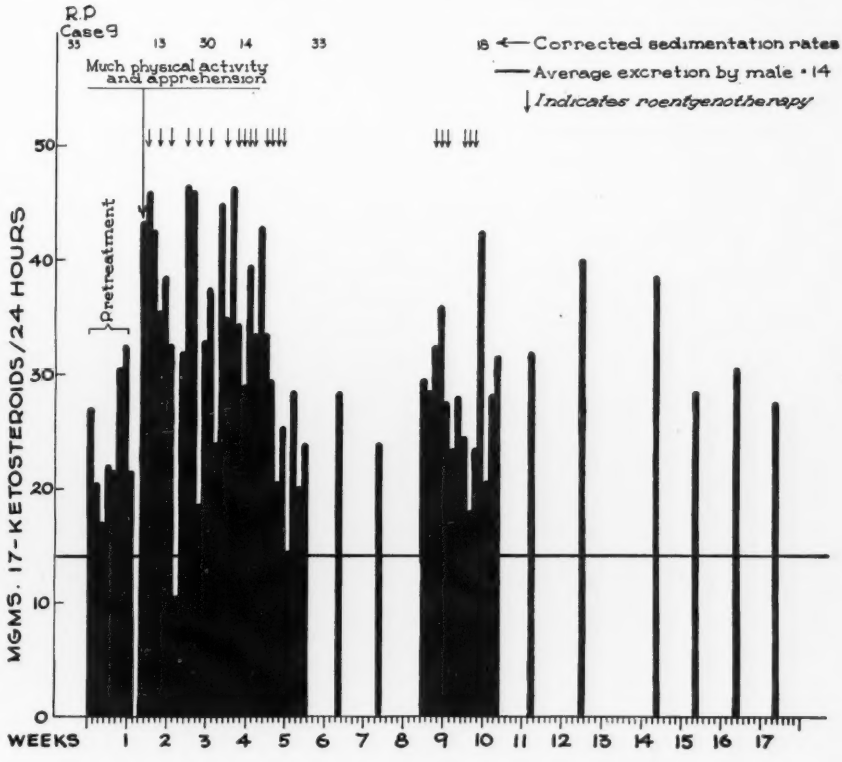

FIG. 2. R.P., case 9. Daily estimations of 17-ketosteroid excretion before, during and after roentgenotherapy.

erage excretion by the males in the spondylarthritis group was 26.7 mg. in 24 hours (Fig. 1). High values were observed in patients before and after roentgenotherapy. Only when there was great malnutrition and a generally poor physical state (W.G., case 25) did the excretion fall to low val-

ues. When W.G. improved clinically following roentgenotherapy, his excretion increased to levels well above normal averages (Fig. 4). Patients who showed few signs of clinical activity and slow progression of the disease had levels which could be in the range of normal excretion values. Patients with evidence of rapidly progressing disease, even when the history indicated short duration, had rather high excretion values.

R.P., case 9. Figure 2, depicts the daily 17-ketosteroid excretion over a period of seventy days in this 25-year-old male who had been ill for less

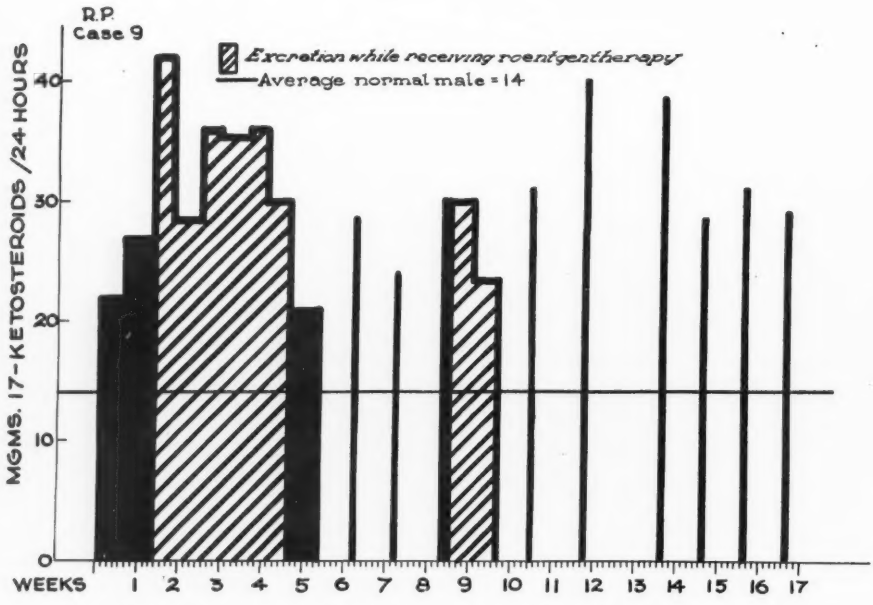

FIG. 3. R.P., case 9. Composite of Figure 2 showing 17-ketosteroid excretion in relation to days of roentgenotherapy.

than a year but was rapidly progressing to total invalidism. He had complete obliteration of the lumbar lordotic curve, marked spasm of the erector spinae muscles, great limitation of spine movement, chest expansion of one-half an inch, and the characteristic gait of such patients. Roentgenograms showed evidence of the disease only in the sacroiliac joints. Upon completion of the first course of roentgenotherapy symptoms were completely relieved, spinal movement became free, and chest expansion increased to three inches. Increased 17-ketosteroid excretion occurred the day preceding roentgenotherapy, coincident with anxiety and extra physical activity, a phenomenon which has been previously observed. A pro-

nounced fall in excretion occurred coincident with side effects of the treatment: nausea, consequent inactivity of the patient, diminished fluid and food intake. The urine volume during that 24 hours was only 750 cc. after a previous average of 1500 cc. Chou (2) and Forbes (3) have commented on the variability of 17-ketosteroid excretion in sick individuals compared with the relative constancy of excretion by normal persons. Figure 3 shows averages of excretion for several consecutive days in R.P.

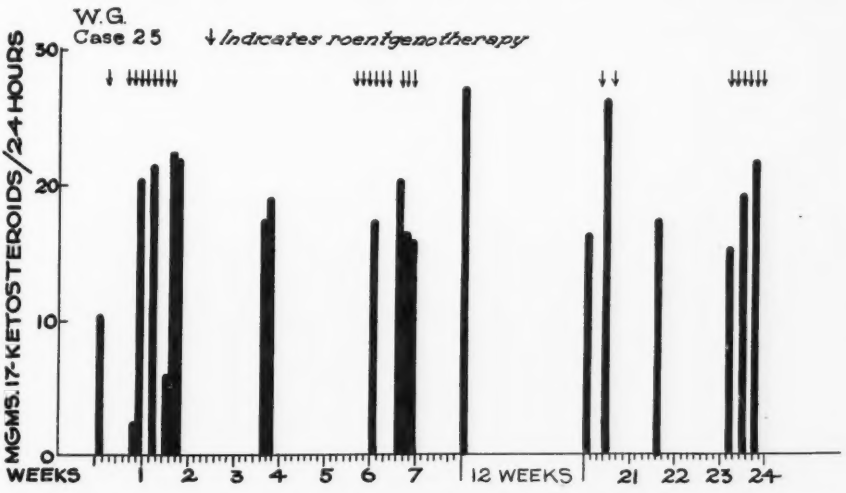

FIG. 4. W. G., case 25. 17-Ketosteroid excretion before, during and after roentgenotherapy—150 rhegmas (skin roentgens) on days shown.

These block out the daily variations and thereby give a better picture of the series of events in Case 9.

W.G. (*case 25, Figure 4*) was admitted to the hospital by ambulance. He was unable to walk, had severe malnutrition, muscle atrophy, spinal rigidity, and mental depression. Roentgenograms showed advanced changes characteristic of spondylarthritis throughout the spine. As Figure 4 demonstrates, the initial urine content of 17-ketosteroids was only 10.5 mg. in 24 hours' excretion. Lower levels of excretion followed roentgenotherapy. Clinical improvement and relief of pain resulted from the first course of roentgenotherapy, and 17-ketosteroid values returned to levels above the average for normal males.

L.N. (*case 7, Figure 5*): In this patient there appeared to be no increased 17-ketosteroid excretion following the roentgen stimulus. The variations in excretion furnished no conclusive evidence of x-ray effect. No urine specimens could be obtained between the second and third courses of roent-

genotherapy. When the patient returned for the third course, he stated he had been entirely free of symptoms following the second course of treatment. At this time it is seen there were higher excretion values than when the patient was first observed.

W.P. (*case 1, Figure 6*): This patient, a robust, well-nourished white male, had only minimal physical signs and mild symptoms of spondylar-

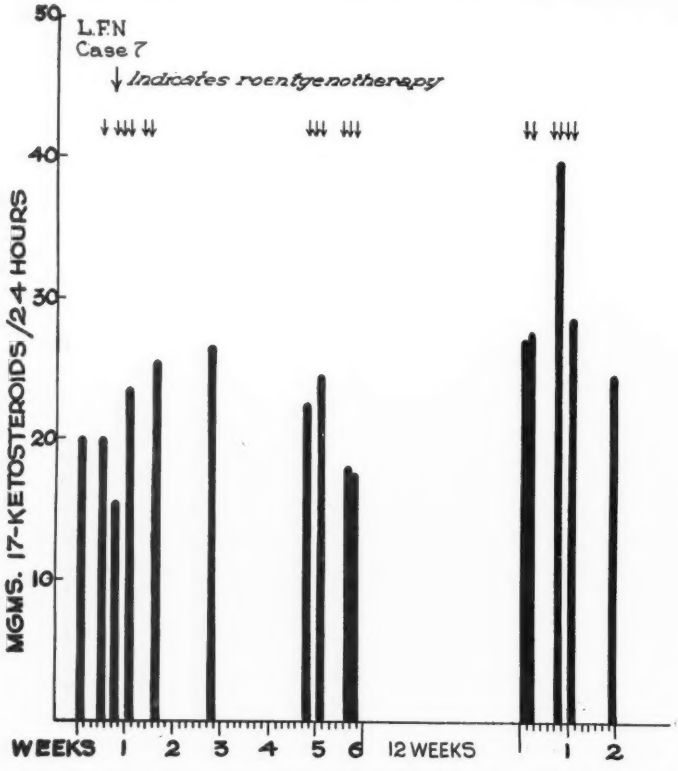

FIG. 5. L.N., case 7. 17-Ketosteroid excretion before, during and after roentgenotherapy—150 rhegmas (skin roentgens) on days shown.

thritis. The moderately high 17-ketosteroid excretion was enhanced initially coincident with roentgenotherapy and a further increase occurred during the second course of treatment.

In each of cases 12, 15, and 31 urine specimens were collected and pooled for three days. Estimations were then made on the total amount, and the average excretion for a 24-hour period was calculated from the result obtained on the pooled specimen. No graphs are presented of these studies. It

can be said, however, that the patient in case 12 showed an average excretion for three days preceding roentgenotherapy of 34 mg. in 24 hours. During the first three days of roentgenotherapy, the urinary excretion of 17-ketosteroids averaged 32.5 mg. The succeeding 3-day pools averaged

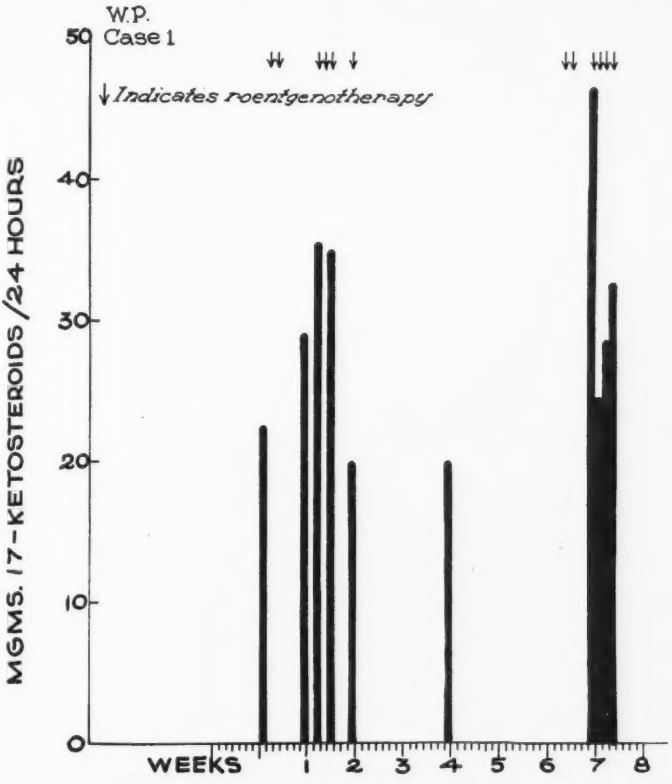

FIG. 6. 17-Ketosteroid excretion before, during and after roentgenotherapy—150 rhegmas (skin roentgens) on days shown.

24 mg., 32 mg., 26 mg., 37 mg., and 29 mg. At the end of the first course of treatment and during the following three weeks no definite improvement in symptoms occurred; nor was there any lessening in severity of physical signs. Stiffness and muscle spasm continued. G.E., case 15, had an initial 17-ketosteroid excretion of 34.5 mg. in 24 hours, although the patient was acutely ill and had a hematocrit reading of 38 per cent and a corrected sedimentation rate of 35 mm. at that time. Roentgenotherapy was given every other day. The 17-ketosteroid excretion after the first treatment increased to an average of 42 mg. in 24 hours for the three-day pool. How-

ever, after three treatments, excretion fell first to the pretreatment level, and then to 13 mg.

SUMMARY

Urinary 17-ketosteroid excretion was found to be increased in spondylarthritis of the ankylosing type in both male and female patients.

High values continued for long periods of time and approached lower levels only when the patient reached a state of exhaustion. Roentgenotherapy seemed to provide a stimulus for increased excretion followed by a relative decrease. Following the roentgenotherapy the values returned to high levels although the symptoms and signs of the disease had abated.

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THE EFFECT OF VITAMIN E IN THE MENOPAUSE

RITA S. FINKLER, M.D.

From the Department of Endocrinology, Newark Beth Irsael Hospital, Newark, New Jersey

THE value of estrogens in the treatment of the symptoms of the menopausal syndrome is firmly established; however, as is well known, there are several contraindications to their use. For instance, most clinicians believe that estrogenic therapy should be avoided in the treatment of women with a familial or personal history of mammary or genital malignancy. Furthermore, in patients who are suffering from precancerous lesions estrogens seem contraindicated. In such cases and when sedation fails, physicians must resort to other therapeutic agents.

Testosterone compounds (1, 2) and a synthetic vitamin E preparation (3) have been employed. Since testosterone propionate has not been effective in our experience, we decided to determine the merits of synthetic vitamin E in combating the symptoms of the menopause.

It is the purpose of this paper to report our observations.

MATERIAL AND METHOD

Sixty-six menopausal women whose ages ranged from 35 to 68 years were studied. The patients presented themselves with the usual train of symptoms such as hot flashes and sweats, vertigo, headaches, parasthesias, fatigue, insomnia and nervousness. In 59 of the women it was deemed advisable to avoid estrogenic therapy because of the clinical findings or the history. Vitamin E[1] therapy therefore was instituted (Table 1).

In the remainder of the patients there was no contraindication to the use of estrogens, and vitamin E was administered either preceding or following estrogenic therapy for the purpose of comparing the results.

The daily dose of vitamin E ranged from 20 to 100 mg.: the average was 30 mg. in divided doses. Therapy was continued for periods ranging from ten days to seven months, with an average duration of thirty-one days. The total dose of vitamin E administered ranged from 280 to 6,300 mg.

In order to rule out a psychologic influence, placebo tablets simulating the vitamin E tablets in all respects were substituted in 17 cases.

Vaginal smears were studied in 45 patients with the purpose of determining any possible hormonal effect on the vaginal epithelium.

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[1] Synthetic vitamin E, in the form of tablets of Ephynal Acetate, 10 mg. each, were supplied through the courtesy of Dr. Elmer Sevringhaus and Dr. Leo Pirk of Hoffmann-La Roche, Inc., Nutley, New Jersey.

TABLE 1. CLINICAL FINDINGS OR HISTORY MILITATING AGAINST THE USE OF ESTROGENS IN 59 MENOPAUSAL PATIENTS

	No. of patients
Uterine fibroids	15
Postradiation castration	4
Cervical carcinoma	2
Carcinoma of breast	2
Chronic cystic mastitis	1
Functional uterine bleeding	2
Uterine bleeding induced by estrogens	5
Prolonged estrogenic therapy	7
Intolerance to estrogens	3
Cervical polyp and endometrial hyperplasia	1
Advanced age (60–68 years)	7
Leukoplakia vulvae	2
Neuromuscular disturbances	3
Premenopausal state	5

are classified as excellent, good, fair or unsatisfactory, according to definite standards. The response was considered excellent when there was complete relief of symptoms and an added sense of well-being; results were classified as good when there was almost complete relief of symptoms and a moderate sense of well-being; and as fair when there was only partial relief of symptoms. When no relief was obtained, the results were termed unsatisfactory.

As seen in Table 2, 31 patients or 47 per cent obtained good to excellent results; 16 or 24.2 per cent obtained fair relief, and 19 or 28.8 per cent were not benefited. Among the latter there were 5 patients who complained of aggravation of symptoms. In two others side effects occurred, which con-

RESULTS

The results obtained with vitamin E therapy are listed in Table 2. They

TABLE 2. RESULTS OBTAINED IN 66 MENOPAUSAL PATIENTS TREATED WITH VITAMIN E

	No. of patients	Per cent of patients
Excellent	5	7.6
Good	26	39.4
Fair	16	24.2
Unsatisfactory	19	28.8

sisted mainly of ocular symptoms (burning of the eyes, spots before the eyes, blurred vision and heaviness of the eyelids).

Two illustrative cases are presented; one demonstrating the beneficial results of vitamin E therapy with placebo control and the other, the failure of vitamin E therapy.

Case. E.W. (*No. 31 in Table 3*), a 48-year-old married woman, was seen on July 22, 1947 with the chief complaints of hot flashes, sweats and headaches of four years' duration. These followed the use of radium for cervical carcinoma and were increasing in intensity to the point where they were occurring 8 to 10 times daily. Physical examination findings were normal and revealed no evidence of the previous cervical carcinoma. Vaginal smears were also free of carcinoma cells. Due to the previous history of carcinoma, estrogenic therapy was contraindicated and therefore the patient was placed on synthetic vitamin E therapy, 10 mg. t.i.d., p.c. Within a week the patient reported improvement in the severity and decrease in the frequency of the symptoms. When the medication was increased to 20 mg. t.i.d., there was a complete disappearance of her hot flashes and sweats. After five weeks of vitamin E therapy, it was decided to substitute placebo medication in order to evaluate the role which psychogenic influence might have played. There was a prompt recurrence of her original complaints within a week. Re-institution of vitamin E therapy once again caused a subsidence of the complaints.

Case Y.F., a 43-year-old unmarried woman, was seen on August 14, 1947, with the chief complaint of hot flashes and sweats of two years' duration, following the use of radiation therapy for a uterine fibroid with meno-metrorrhagia. Although estrogens had controlled these menopausal symptoms, this medication had to be discontinued periodically because of recurrence of moderate bleeding. Vitamin E (10 mg. t.i.d.) was administered for two weeks. Although the bleeding stopped, hot flashes and sweats recurred. An increase of the dosage of vitamin E to 20 mg. t.i.d. for another three-week period also had no therapeutic effect. Vitamin E was discontinued and sedatives were substituted, with partial relief of symptoms.

Those patients who benefited from vitamin E therapy and who later discontinued the medication experienced a recurrence of all their symptoms after a period of from three days to one month. Reinstitution of vitamin E therapy resulted again in relief of symptoms. Placebo medication was substituted for the vitamin E preparation in 17 patients who had obtained good results from vitamin E therapy. All had a recurrence of symptoms and relief ensued when vitamin E was reinstituted (Table 3). It is important to note that 3 patients who were not included in this series continued to claim good results with inert material, after vitamin E was withdrawn.

TABLE 3. EFFECT OF PLACEBO SUBSTITUTION IN 17 PATIENTS TREATED WITH VITAMIN E

Case No.	Age Yrs.	Symptoms	Vitamin E therapy			Placebo therapy	
			Duration	Total amount	Results	Duration	Results
				mg.			
#16 A.M.	68	Hot flashes, sweats, chills	2 months	1800	Excellent	2 weeks	Recurrence of symptoms
#17 E.M.	48	Hot flashes, menorrhagia	2 weeks	420	Good	"	"
#18 D.V.	43	Headaches, hot flashes, vertigo, menorrhagia	3 weeks	630	Good	"	Recurrence of symptoms on 3 different occasions
#20 C.M.	47	Hot flashes, sweats, headaches	2 weeks	420	Good	"	Recurrence of symptoms
#21 G.S.	49	Hot flashes, vertigo, fatigue, irritability	4 weeks	900	Excellent	"	"
#23 K.V.	48	Hot flashes, sweats	2 weeks	420	Good	"	"
#30 K.D.	51	Hot flashes	7 weeks	2940	Good	"	"
#31 E.W.	48	Hot flashes, sweats (postradiation)	5 weeks	1684	Excellent	1 week	"
#33 K.R.	50	Hot flashes, headaches, vertigo	4 weeks	1290	Fair	2 weeks	"
#37 B.W.	50	Hot flashes, sweats, numbness, headaches	3 weeks	630	Fair	"	"
#38 P.Z.	50	Hot flashes	3 weeks	630	Good	"	"
#39 A.M.	48	Hot flashes, headaches, crying spells (postradiation)	2 weeks	420	Good	"	"
#43 H.J.	59	Hot flashes	4 weeks	840	Good	"	"
#55 H.P.	50	Hot flashes, headaches, fatigue, parasthesia, emotional disturbances	3 weeks	630	Good	"	"
#58 K.B.	46	Headaches, insomnia, dyspnea, menorrhagia	6 weeks	2520	Good	"	"
#59 G.G.	46	Hot flashes, sweats, headaches, insomnia, parasthesia	3 weeks	630	Good	"	"
#64 E.K.	57	Hot flashes, sweats, headaches	6 weeks	1260	Good	"	"

Physical examination revealed no changes in the breasts or the uterus in any of the patients. Similarly, no effect on the vaginal epithelium was detected by studying the vaginal smear picture according to the method developed by Papanicolaou. Therefore, with this type of therapy, the vaginal smear cannot be utilized as an index of the therapeutic effect.

DISCUSSION

As mentioned previously, a familial or personal history of malignant disease constitutes a contraindication for the use of estrogens. Also, it seems wise to avoid them in patients with precancerous conditions with uterine fibroids, cervical polyps, fibroadenomata of the breast or chronic cystic mastitis. Furthermore, there are women in whom the menopausal syndrome is characterized by meno-metrorrhagia; and women in whom the administration of follicular hormone produces vaginal bleeding. In these groups also, estrogenic therapy should not be employed. In addition, it has been reported (4) that patients of advanced age (past 60) may develop pathologic tissue changes under the influence of prolonged estrogenic therapy. Finally, in that group of patients with menopausal vasomotor disturbances who still have normal cycles, it is inadvisable to use estrogens because of the danger of producing prolonged irregular menses.

Christy (3) was the first to use vitamin E in the menopause. He employed this therapy in an attempt to relieve menopausal discomfort in 25 patients with a definite diagnosis or a strong suspicion of neoplastic disease. According to him, "the entire group of cases responded to the treatment and showed either complete relief or very marked improvement with less frequency and less severity of the hot flashes and drenching perspiration, and a definite change for the better in their mood and outlook." Christy also states that in some of the cases relief of vasomotor instability was more easily obtained with the use of vitamin E than with the estrogens. While we are in agreement with this investigator that vitamin E constitutes a valuable means of controlling menopausal symptoms, it certainly is not effective in all cases as can be seen in Table 2. We also feel that estrogens give more rapid and more complete relief than vitamin E in most cases. This observation was made in the 7 cases in which vitamin E was administered either preceding or following estrogens for the purpose of comparison. However, vitamin E therapy is the medication of choice in cases in which the use of estrogens is contraindicated.

SUMMARY AND CONCLUSIONS

1. Vitamin E therapy was instituted in 66 selected and controlled patients who complained of the characteristic vasomotor symptoms of the

A RAPID COLORIMETRIC METHOD FOR THE DETERMINATION OF SODIUM IN BIOLOGICAL FLUIDS

JOSEPH W. GOLDZIEHER, M.D. AND
GILBERT C. H. STONE, PH.D.

From the Research Division and Endocrine Clinic, St. Clare's Hospital, New York and the Department of Chemistry, the City College of New York

THE clinical importance of sodium metabolism becomes increasingly evident with every year. However, widespread investigation in this field has been severely restricted because of the absence of a generally useful method for sodium determination, i.e., one which requires no specialized equipment, unusual technical skill, or great expenditure of time and which may therefore be fitted into the routine of the general clinical laboratory.

The speed and sensitivity of the flame photometer, for instance, are largely offset by its capriciousness: the problem of flame stability has not yet been overcome, with the result that the reproducible accuracy in expert hands is only 5 to 10 per cent and that "frequently an hour or more is required to establish conditions of equilibrium for the desired range of concentration" (1). Also, the cost of such instruments at the present time may be prohibitive. A sensitive nephelometric technique has been described (2) but this seldom-used method also requires an instrument which is not commonly available. Purely chemical methods are based on the formation of relatively insoluble acetates of sodium with uranium and zinc or uranium and magnesium, having the formulae $NaZn(UO_2)_3(CH_3COO)_9 \cdot 9(?)H_2O$ and $NaMg(UO_2)_3(CH_3COO)_9 \cdot 9(?)H_2O$. Modifications (3, 4, 5) of the older gravimetric technique for measuring the triple salt have speeded up the procedure, though sometimes with a great sacrifice of sensitivity (4). The otherwise excellent method of Consolazio and Dill (5) requires ashing, which is a long and tedious process.

All these chemical methods are limited by the same basic obstacle, namely the low color intensity of the sodium triple salt. Recognizing this, color intensification with potassium ferrocyanide (6) has been attempted, but the ferrocyanide reaction has been criticized repeatedly as being highly susceptible to changes in temperature and to excesses of the reagents. The use of ammonium thiocyanate (7) serves only to stabilize the color of the triple salt, but has no intensifying action.

In 1929 Rosenheim and Daehr (8) found that an intense yellow-to-red color was produced by the action of hydrogen peroxide on alkaline solutions

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menopause. Good to excellent results were obtained in 31 women, and fair results in 16. In 19 patients the treatment was ineffectual.

2. Discontinuance of the vitamin E preparation was attended by prompt recurrence of symptoms with relief resulting again on reinstitution of the medication.

3. Substitution of placebo medication for the vitamin E preparation in 17 patients caused a recurrence of symptoms.

4. No changes in the breasts, uterus or vaginal epithelium were noted during vitamin E therapy. Side effects were negligible and there were no contraindications to its use.

5. Vitamin E is a valuable aid in the treatment of menopausal patients in whom estrogens are contraindicated.

Acknowledgment

I gratefully acknowledge the cooperation of my associates on the Endocrine Service, Drs. Zelda Marks, George M. Cohn, Gertrude Oberlander, and Sylvia F. Becker.

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of the uranyl ion. This reaction was studied by Arnold and Pray (9) who found that it followed Beer's law and was therefore suitable for quantitative spectrophotometry. In the course of our investigation we were able to corroborate this aspect of their work. Even though the exact nature of the hydrated uranyl oxide ion in alkaline solution is unknown, it has been possible to use it in developing a rapid and extremely sensitive colorimetric method suitable for biological fluids.

METHOD

Reagents

1. Uranyl zinc acetate reagent. Add 77 Gm. of uranyl acetate to 750 ml. distilled water and 14 ml. glacial acetic acid which have been heated nearly to boiling. To this mixture is added 231 Gm. of zinc acetate, divided into five or six portions, with frequent stirring. Finally, 7 ml. of glacial acetic acid is added and the solution is allowed to cool. After cooling, the reagent is diluted to 1 liter with distilled water and 200 ml. of 95 per cent ethyl alcohol is added. The solution is refrigerated overnight, filtered, and is then ready for use.
2. Sodium triple salt. To 10 ml. of the above solution is added an excess of a concentrated solution of sodium chloride. The precipitate is collected by filtration, washed five times with glacial acetic acid and five times with ether.
3. Wash reagent. A solution of 425 ml. of 95 per cent ethyl alcohol and 75 ml. glacial acetic acid is saturated at room temperature with the sodium triple salt (see above). This solution is kept in a brown bottle.
4. A saturated solution of mercuric chloride in 95 per cent ethyl alcohol.
5. A saturated aqueous solution of ammonium carbonate.
6. A 30 per cent solution of hydrogen peroxide ("Superoxol").
7. Powdered calcium hydroxide.

Filtrates

1. Urine. To approximately 10 ml. urine add 3 drops of mercuric bichloride solution, shake and let stand for a few minutes. Then add a spatula-tipful of calcium hydroxide powder, shake well, then filter.
2. Serum. To 3.0 ml. of 10 per cent trichloracetic acid add 1.0 ml. serum, dropwise. Shake, and centrifuge or filter.

Procedure

Pipette 0.25 ml. of the urine filtrate or 1 ml. of the serum filtrate into a 15 ml. centrifuge tube and add 5 ml. of the uranyl zinc reagent. Mix by twirling the tube and allow to stand for 20 minutes. The tubes should be agitated briefly at least twice during this interval. Centrifuge at high speed for 7 minutes, then decant the supernatant fluid and drain for 1 minute. Expel 5 ml. of the wash reagent onto the precipitate, washing down the sides of the centrifuge tube during the process. Centrifuge for 7 minutes, decant and drain. Dissolve the remaining precipitate with a few drops of distilled water, add 6 ml. of the saturated ammonium carbonate solution and 1 ml. of the 30 per cent hydrogen peroxide in that order, and dilute to 15 ml., or to 25, 50 or 100 ml. by transfer to a suitable volumetric flask with washings. The appropriate final dilution (i.e., 15, 25, 50 or 100 ml.) depends on the sensitivity of the colorimeter to be used. The correct dilution for the individual instrument is the one which gives to the desired range of values the greatest

spread on the meter or dial of the instrument.) Mix by inversion and read in the colorimeter using a filter with maximum transmittance at 415–430 mμ.

EXPERIMENTAL DATA

Absorption spectrum

The absorption spectra of two different concentrations as determined with a Beckman spectrophotometer model DU are shown in Figure 1. These curves are quite different in shape from those of Arnold and Pray, who found transmittance minima in the region of 400 to 460 mμ. The curves obtained by us show no minima even though measurements were carried almost into the ultraviolet. This difference in the absorption spectra is in all

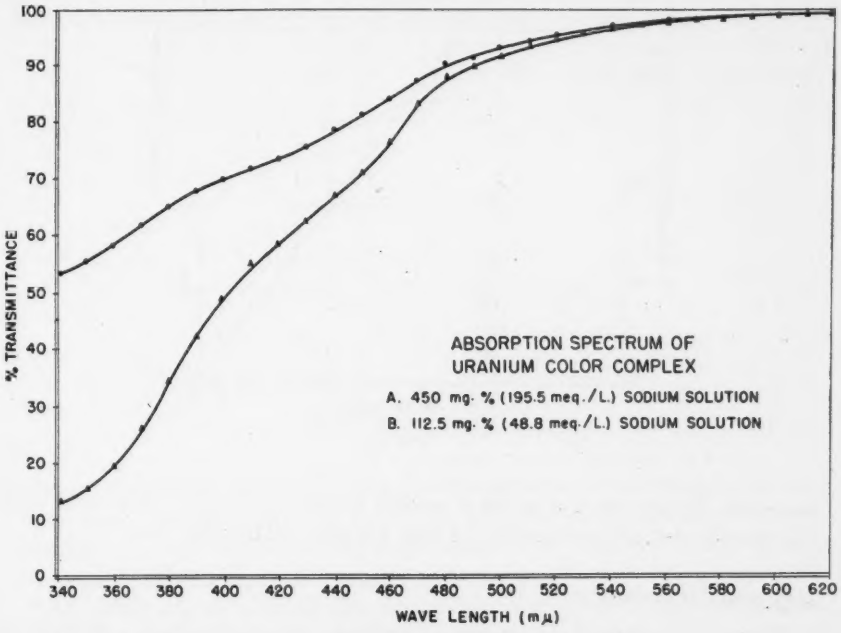

FIG. 1

probability due to the different dilutions employed by Arnold and Pray and ourselves. Their two curves represent 0.3 and 1.3 mg. of sodium respectively whereas ours, recalculated in terms of their technique, represent 0.09 and 0.0225 mg. On the basis of Figure 1 it is evident that the shorter the wavelength (in the visible region), the greater the sensitivity. For practical application in colorimeters, filters with a maximum transmittance in the region of 415 to 430 mμ are readily available and have been found entirely satisfactory.

A calibration curve is shown in Figure 2. Calibrations have always been carried out by precipitating and developing standard solutions of sodium (chloride) in 6 per cent trichloracetic acid, according to the method described. In the range of serum sodium concentrations, the sensitivity is 11 mg. per cent (4.8 mEq./L.) per scale division, using a Leitz-Rouy col-

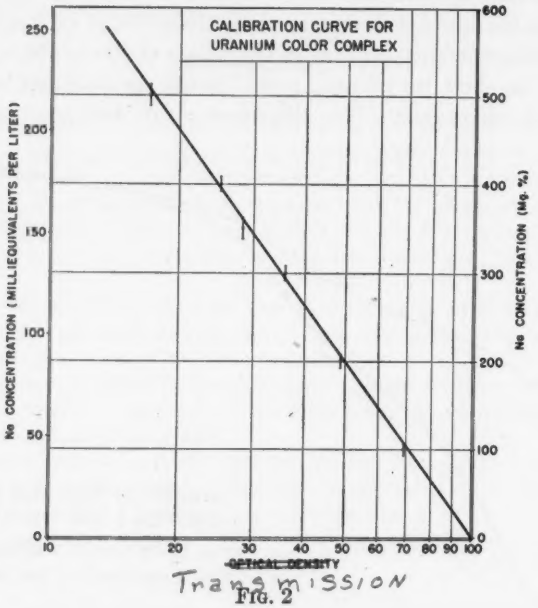

FIG. 2

orimeter. Estimates of a tenth of a scale division are made with ease, making the theoretical sensitivity 1.1 mg. per cent (0.5 mEq./L.).

Reproducible accuracy

This was studied by numerous triplicate determinations, a typical example of which is reproduced in Table 1. In some cases, known dilutions of the sodium triple salt were developed for color and in others, various known amounts of sodium were added to serum and carried through the entire procedure (Table 1). Data obtained by both these methods indicate a reproducible accuracy of 3 per cent.

Procedure

The substances which interfere with quantitative triple salt formation are protein, phosphate, arsenate, lithium, and large amounts of potassium

(10). In biological fluids, only the protein and phosphate are of importance.

Removal of protein from serum and spinal fluid is accomplished by the use of trichloracetic acid. Since serum inorganic phosphate introduces a constant absolute error of only 1 mEq./L. (11) with proportionately small changes due to variation in the serum phosphate level, this factor is usually ignored.

In urine, mercuric chloride is used for protein precipitation; trichloracetic acid would of course be incompatible with the calcium hydroxide. Some workers (2) have found that refrigeration is adequate for the removal of

TABLE 1

Sample	Meter reading	Observed (mEq./L.)	Calculated (mEq./L.)	Error (per cent)
1.0 ml. serum	32.5			
#1–83	34.9			
	33.0			
	(av. 33.5)	137		(av. 2.4)
1.0 ml. serum	29.9	151		1.9
#1–83 plus 40 mg.	30.0	150	154	2.6
(17 mEq.) sodium	32.0	147		4.5
0.5 m. serum	33.0	138		3.0
#1–83 plus 150 mg.	33.1	138	134	3.0
(65 mEq.) sodium	33.1	138		3.0

urinary phosphate. However, this procedure is time-consuming. We have found that calcium hydroxide serves the purpose far better, for it requires no extra time and does not complicate matters by causing changes of urine volume due to temperature.

The efficiency of washing was studied by means of 10 pairs of precipitates, half of which were washed once with 5 ml. and half twice with 2.5 ml. of the wash reagent. The greater efficiency of the double washing could not be observed by the usual technique in the colorimeter and required special means (a 6 cm. column of fluid) for its demonstration. Another group of 10 precipitates was washed twice with 5 ml. portions of the wash reagent. No perceptible increase in color density of the second washing over that of unused wash reagent could be demonstrated.

With proper centrifuging, no difficulty was encountered in packing the precipitate firmly, and with these small amounts of precipitate no troublesome flotation of crystals (as found by Bradbury) occurred.

The developed color was tested for stability and no changes were observed during a 2-hour observation period. However, the formation of oxygen bubbles frequently takes place fairly soon after the addition of the hydrogen peroxide. Vigilance must be exercised to dislodge all bubbles before readings are carried out, and it was found advantageous to carry out the readings as promptly as possible in order to avoid this nuisance.

SUMMARY

A rapid colorimetric method for the determination of sodium in biological fluids is presented. The method is based on the precipitation of sodium as the triple salt of uranium and zinc acetate, and intensification of the color of the uranyl ion with hydrogen peroxide in alkaline solution. The reproducible accuracy of the method is 3 per cent.

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The Association for the Study of Internal Secretions Announces A Postgraduate Assembly In Endocrinology

OKLAHOMA CITY, OKLAHOMA SKIRVIN HOTEL FEBRUARY 21–26, 1949

The faculty will consist of prominent researchers and clinical endocrinologists in the various branches of the medical sciences, gathered from the United States and Canada and will include the following:

Dr. Willard M. Allen, Professor and Head, Department of Obstetrics and Gynecology, Washington University School of Medicine.

Dr. Edwin B. Astwood, Research Professor of Medicine, Tufts College.

Dr. J. S. L. Browne, Professor of Medicine, McGill University.

Dr. Edward A. Doisy, Professor and Head, Department of Biochemistry, St. Louis University School of Medicine.

Dr. Roberto Escamilla, Associate Clinical Professor of Medicine, University of California Medical School.

Dr. E. C. Hamblen, Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine.

Dr. Laurence W. Kinsell, Associate Clinical Professor of Medicine, University of California Medical School.

Dr. C. N. H. Long, Sterling Professor of Physiological Chemistry and Dean, Yale University School of Medicine.

Dr. Cyril M. MacBryde, Associate Professor of Clinical Medicine, Washington University School of Medicine.

Dr. E. Perry McCullagh, Chief, Dept. of Endocrinology and Metabolism, Cleveland Clinic.

Dr. Harold L. Mason, Professor, Physiological Chemistry, Mayo Foundation, University of Minnesota.

Dr. Warren O. Nelson, Professor of Anatomy, University of Iowa College of Medicine.

Dr. Edward Rynearson, Associate Professor of Medicine, Mayo Foundation, University of Minnesota.

Dr. Hans Selye, Professor of Experimental Medicine, University of Montreal.

Dr. E. Kost Shelton, Associate Professor of Medicine, University of Southern California.

Dr. Paul M. Starr, Clinical Professor of Medicine, University of Southern California.

Dr. Willard O. Thompson, Clinical Professor of Medicine, University of Illinois College of Medicine.

Dr. George Thorn, Hershey Professor of the Theory and Practice of Physic, Harvard Medical School.

Dr. Henry H. Turner, Associate Professor of Medicine, University of Oklahoma School of Medicine.

Dr. Lawson Wilkins, Associate Professor of Pediatrics, Johns Hopkins Hospital.

This course will be a practical one of interest and value to the specialist and those in general practice. The program will consist of lectures, clinics and demonstrations. Ample time will be given to questions and answers at the end of each session, and registrants are encouraged to contact members of the faculty for individual discussions.

A fee of $100 will be charged for the entire course and the attendance will be limited to 100. REGISTRATION WILL BE IN THE ORDER OF CHECKS RECEIVED. Should there be an insufficient number of applicants to fill the course, the registration fee will be immediately refunded in its full amount.

Please forward application on your letterhead, together with check, payable to The Association for the Study of Internal Secretions, to Henry H. Turner, M.D., Chairman of the Postgraduate Committee, 1200 North Walker Street, Oklahoma City, Oklahoma, before February 1, 1949.

Applicants should make reservations directly with hotels of their choice. Some of the better downtown hotels in Oklahoma City, listed according to their proximity to the Skirvin are: Skirvin Tower, Huckins, Wells-Roberts, Biltmore and Black.

ANNOUNCEMENT OF NATIONAL RESEARCH COUNCIL GRANTS FOR RESEARCH IN ENDOCRINOLOGY

The Committee on Research in Endocrinology, National Research Council, wishes to announce that requests for grants-in-aid during the fiscal period from July 1, 1949, to June 30, 1950, will be received until February 28, 1949. Application blanks may be obtained by addressing the Secretary, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. In addition to a statement of the problem and research plan or program, the Committee desires information regarding the proposed method of attack, the institutional support of the investigation and the uses to be made of the sum requested. No part of any grant may be used by the recipient institution for administrative expenses.

The Committee makes grants-in-aid of research in the general field of experimental and clinical endocrinology. However, applications for support of research in the problems of sex in the narrower sense cannot be given favorable consideration, and investigators seeking support in this field should direct their proposals to the Committee for Research in Problems of Sex of the National Research Council. The Committee on Research in Endocrinology, however, will continue to give consideration to the support of studies of the effect of sex hormones on non-sexual functions, *e.g.*, on general metabolism and on the metabolism of steroid hormones.

The 1949 Meeting of the Association for the Study of Internal Secretions

The Thirty-First Annual Meeting of the Association for the Study of Internal Secretions will be held in the Chalfonte-Haddon Hall, Friday and Saturday, June 3 and 4, 1949, in Atlantic City, New Jersey.

We are informed by the hotel management that reservations will be difficult to secure on short notice; therefore, members are urged to make reservations at once with Chalfonte-Haddon Hall, giving time of arrival and length of stay in Atlantic City.

The scientific sessions will be held in the Viking Room, as formerly, and registration will be on the same floor. The annual dinner will be held in the Rutland Room, Friday, June 3, at 7 p.m., preceded by cocktails in the same room.

Those wishing to present papers, which will be limited to ten minutes, should send the title and four copies of an abstract of not more than 200 words, to Dr. J. S. L. Browne, Royal Victoria Hospital, Montreal 2, Canada, not later than March 1, 1949. It is imperative that the abstracts be informative and complete, with results and conclusions, in order that they may be of value for reference and suitable for printing in the program.

Nominations for the Squibb and Ciba Awards and the Ayerst, McKenna and Harrison Fellowship should be filed on special forms with the Secretary of the Association, not later than March 15, 1949, according to specifications given in the section on Awards.

The Awards of the Association for 1949

Nominations for Awards

Three Awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each Award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1949.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori and in 1948 to Dr. Fuller Albright. No award was made in 1943. No age or special limitation is stipulated by the donor of the Award.

THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or preclinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li and in 1948 to Dr. Carl G. Heller. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947 and in 1948 it was given to Dr. Ernest M. Brown, Jr. This Fellowship is designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. The Fellowship may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend for the Fellowship will vary in accordance with the qualifications of the appointee, but will not exceed $2500.00. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals, submit a program of proposed study, indicate one or more institutions where the proposed program shall be carried out and submit statements of approval from the investigators with whom he proposes to conduct his research.

American Goiter Association

THE 1949 MEETING

The next annual meeting of the American Goiter Association will be held at the Loraine Hotel in Madison, Wisconsin, May 26, 27 and 28, 1949.

All members of the Association are urged to make their hotel reservations as early as possible. Those who would prefer a resort hotel will find the new Edgewater very beautiful. It is half a mile from the Loraine on the shores of Lake Mendota.

The officers of the Society are as follows:

President	—Arnold S. Jackson, Madison, Wisconsin
President Elect	—Samuel F. Haines, Rochester, Minnesota
Vice President	—Willard O. Thompson, Chicago, Illinois
Corresponding Secretary	—T. C. Davison, Atlanta, Georgia
Recording Secretary	—Geo. C. Shivers, Colorado Springs, Colorado
Treasurer	—V. E. Chesky, Halstead, Kansas

Executive Councilors

J. H. Means, Boston, Massachusetts
Elmer Bartels, Boston, Massachusetts
Allen Graham, Pittsburgh, Pennsylvania
H. P. Sloan, Bloomington, Illinois
D. U. McGregor, Hamilton, Ontario, Canada

Dr. George Crile, Jr. of Cleveland is Chairman of the Program Committee.

THE VAN METER PRIZE

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Madison, Wisconsin, May 26, 27 and 28, 1949, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, and must be presented in English. A typewritten double spaced copy should be sent to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than March 15, 1949. The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association. This will not prevent its further publication, however, in any journal selected by the author.

Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor: ROY HERTZ. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

PITUITARY

KANTER, A. E., and KLAWANS, A. H.: Shock from posterior pituitary extract, *Am. J. Obst. & Gynec.* **56**: 366–369, 1948.

The authors report 5 instances of shock in association with the use of posterior pituitary extract in thousands of obstetric and gynecologic patients. This shock occurs as a result of the direct pressor action upon the coronary arteries. It is readily combatted by the use of adrenalin chloride or ephedrine sulfate and infusions of fluids, whole blood or blood plasma. Because of the potentialities of shock, the authors favor the use of ergot derivatives in obstetrics. However, for use in gynecologic surgery, they believe there is no adequate substitute for posterior pituitary extract.—*C.D.D.*

THYROID

BOEKELMAN, A. J.: The thyroid as a regulator of potassium metabolism, *Presse méd.* **56**: 23–25, 1948.

The basal metabolism is directly proportional to the potassium content of the erythrocytes. The potassium content is high in hyperthyroidism and drops with iodine treatment as the metabolic rate decreases. Iodine has no influence on the corpuscular potassium in normal persons. The potassium in the plasma is unaffected.—*A.E.M.*

HOLLANDER, G. H., and MANDELBAUM, H.: The treatment of angina pectoris with propylthiouracil, *Ann. Int. Med.* **28**: 1150–1156, 1948.

Ten hypertensive patients with a definite anginal syndrome were studied, (1 male, 9 females). The ages ranged from 45 to 62 years. All patients had been tried on other types of medication without success. Six showed definite symptomatic improvement on 50 to 200 milligrams of propylthiouracil daily. Two of the others became progressively worse. No correlation was noted between improvement and level of the basal metabolic rate. If improvement occurred, it was manifested within 8 weeks of onset of treatment. It was not necessary to produce myxedema to get relief of pain. The authors believe that a further clinical trial of 6-propylthiouracil in angina pectoris is indicated.—*C.D.D.*

HORLICK, L., and HAVEL, L.: The effect of feeding propylthiouracil and cholesterol on the blood cholesterol and arterial intima in the rat, *J. Lab. & Clin. Med.* **33**: 1029–1036, 1948.

In view of previous findings that the thyroid gland is involved in the entire process of

experimental atherosclerosis, propylthiouracil was administered to rats, in an attempt to break down the resistance of this species to the induction of atherosclerosis by cholesterol feeding. In contrast to findings in dogs, propylthiouracil failed to break down the rat's resistance, indicating that it may be dependent on other fcators in addition to the thyroid gland and its secretions. The combination of cholesterol with propylthiouracil produced a synergistic rise in the blood cholesterol levels, an action not clearly understood.—*T.H. McG.*

McCullagh, E. Perry; Hibbs, R. E., and Schneider, R. W.: Propylthiouracil in the treatment of hypothyroidism, *Am. J. M. Sci.* **214**: 545–552, 1947.

Propylthiouracil is a safe drug. In 218 patients treated for an average of 8 months and in some as long as 14 months, no cases of agranulocytosis were seen, in contrast with its occurrence in thiouracil treatment. For this reason the routine practice of taking weekly white blood counts was discontinued. Three minor reactions to propylthiouracil occurred, and 4 other reactions required the cessation of treatment. It was found effective in controlling hyperthyroidism of all types except possible instances of acute crisis in which its reaction is too slow. The hyperthyroidism of acromegaly may also be an exception. An effective dose in more than 95% of the patients was 300 mg. per day. A smaller dose was effective in many, and a larger dose was required in less than 4%. (An effective dose was defined as one which produced a progressive fall in basal metabolic rate of 2% or more per week to within normal range.) Iodine in doses as high as 30 mg. per day may be used concurrently with propylthiouracil. It will eliminate the thrill and bruit in diffuse glands and does not hinder the action of propylthiouracil. The probable frequency of permanent remissions of hyperthyroidism following the use of propylthiouracil can not yet be properly estimated. At present, long-continued use of the drug appears warranted in some patients and may later appear feasible and perhaps desirable in many.

The authors close with a tentative plan for the use of propylthiouracil to the best advantage of the patient with hyperthyroidism, with special regard to age, type of hyperthyroidism and kinds of complications.—*E.C.R., Jr.*

Peters, J. P., and Man, E. B.: The relation of albumin to precipitable iodine of serum, *J. Clin. Investigation* **27**: 397–405, 1948.

Hypoalbuminemia associated with serum iodine deficiency in the absence of definite evidence of hypothyroidism was demonstrated in a series of patients with miscellaneous conditions (cirrhosis of the liver, craniopharyngioma, anorexia nervosa, hypopituitarism, and others) in which hypoalbuminemia appeared to be the only common factor. Administration of active thyroid substance in doses that are effective in the treatment of myxedema failed to raise the precipitable iodine in the serum of these patients; injections of enough salt-poor human albumin to raise considerably their serum albumin did not consistently increase, and more often decreased, the precipitable iodine. Data on 22 cases are tabulated.—*T.H. McG.*

Williams, R. H., and Kay, G. A.: Further studies on the correlation of chemical structure and antithyroid effect, *Am. J. M. Sci.* **213**: 198–205 (Feb.) 1947.

The authors briefly review the work done since 1943, prompted by the early clinical experiences with thiouracil which indicated that serious toxic reactions sometimes oc-

curred. It was hoped that compounds could be found which have stronger antithyroid action, thereby exposing the body tissues to a smaller concentration of the drug, or substances which by their difference in chemical structure were less toxic than thiouracil even though their concentration in the body might be greater. Most of the compounds which the present authors studied were derivatives of thiourea or aniline, in addition to which a few organic sulfur compounds were tested. It was especially desirable to test the antithyroid effect of iodinated thioureas and iodinated aminobenzenes. Experimental animals were rats and chicks.

The most potent antithyroid compounds found were thiouracils with short-chain hydrocarbons in the 6-position, especially the n-propyl derivative. The toxicity of all of the thiouracils was relatively low and caused no significant inhibition of growth.

Of the thioureas none possessed significant activity, with the exception of 2-aminothiazol, though to a much lesser degree than thiouracil.

The activity of several anilides structurally similar to p-amino-benzoic acid was relatively slight, though that of diaminobenzophenone and of p-aminocinnamic acid were fairly great.

The iodinated compounds showed little or no antithyroid effect, besides being relatively toxic.

Combined treatment with para-aminobenzoic acid and thiouracil proved that the amount of goitrogenesis equals, or perhaps exceeds, an additive effect of the two compounds. Many generalizations, made on correlating antithyroid activity with chemical structure, are listed and tabulated.

Finally the authors draw the following conclusions: minor structural changes in the two main series of goitrogenic compounds, thiocarbonamides and aminobenzenes, may modify the activity of these compounds, sometimes causing a marked potentiation of effect, and at other times greatly decreasing or abolishing the effect. The C=S linkage is essential, and usually without substituents attached to the sulfur. In most instances this linkage is adjacent to two amino groups, although activity can exist when one of the amino groups is replaced by an oxygen or sulfur grouping. Closure of thiourea chains generally causes a potentiation of effect. Additions of short-chain hydrocarbons tend to augment the effect of thiouracil, when attached to the 6-position. Thus far, iodination of the thiourea amino-benzene derivatives has not augmented the goitrogenic effect. The simultaneous ingestion of thiouracil and p-aminobenzoic acid appeared to result in an additive effect.—*E.C.R., Jr.*

ADRENALS

CAHILL, G. F.: Pheochromocytomas, *J.A.M.A.* **138:** 180 (Sept. 18) 1948.

Four carefully studied cases of pheochromocytoma are described in detail and others referred to briefly. The associated hypertension was sustained in two cases, the B.M.R. was markedly elevated in two cases. Hyperglycemia and glycosuria were not marked in the younger patients. Three cases were in children and one case was associated with Cushing's syndrome. Several of the tumors were extra-adrenal and one was multiple; the intra-adrenal ones were well visualized by x-ray after perirenal air insufflation. All cases showed a drop in blood pressure after the injection of benzodioxane. The danger of operation is lessened by the use of tri-brom-ethanol in anaesthesia induction, by occluding the blood supply to the tumor before handling it, and by the infusion of epinephrine and occasionally adrenal cortical extract after the tumor has been removed.—*A.P.F.*

THORNE, G. W.; FORSHAM, P. H.; PRUNTY, F. T. G., and HILLS, A. G.: A test for adrenal cortical insufficiency, *J.A.M.A.* **137**: 1005 (July 17) 1948.

A reliable and sensitive test for adrenal cortical insufficiency is presented. Two striking and easily determined changes (a decrease of 50 or more per cent in circulating eosinophils and a rise in excretion of uric acid) consistently follow the administration of a single dose of adrenocorticotropic hormone to normal subjects and patients with diseases not involving the adrenal cortex. A decrease of 50 or more per cent in the urinary uric acid-creatinine ratio indicates adequate adrenal cortical reserve. The few conditions in which the test is not useful are described.—*A.P.F.*

FRIEDMAN, S. M.; FRIEDMAN, C. L., and POLLEY, J. R.: Potentiation of the hypertensive effects of desoxycorticosterone acetate by various sodium salts, *Am. J. Physiol.* **153**: 226–234, 1948.

The action of sodium chloride in intensifying the effects of DCA on renal function, blood pressure and electrolyte pattern seems specifically referable to the sodium ion. Phosphate may be excessively damaging to the kidney under the influence of DCA. The electrolyte derangement is parallel to the kidney injury. The renal damage caused by salt and DCA is not necessarily accompanied by an increase in hypertension. The increase in blood pressure caused by DCA precedes changes in renal function.—*A.E.M.*

WATERHOUSE, C., and KEUTMANN, E. H.: Kidney function in adrenal insufficiency, *J. Clin. Investigation* **27**: 372–379, 1948.

Thirteen patients with adrenal insufficiency were studied with respect to glomerular filtration rate, renal plasma flow and maximum excreting capacity. All patients were in good clinical condition and controlled either on salt alone or with desoxycorticosterone acetate. Treatment, in therapeutic doses, with desoxycorticosterone acetate, testosterone propionate, aqueous adrenal cortical extract, extract of pork adrenal cortex in oil and desiccated thyroid substance was superimposed when possible and renal function studies were carried out. The rates of glomerular filtration were below normal in all patients at all times. Treatment with the hormones resulted in little if any improvement above that found when salt was used in adequate, therapeutic amounts. Large amounts of extract of adrenal cortex resulted in slight increase in filtration rate but the values were still far below normal. The effective renal plasma flow was reduced in all patients except in two cases with a moderate anemia. No change was noted in renal plasma flow by the addition of specific hormonal therapy. The maximum tubular excretory capacity was low in all female patients and normal in all male patients with the exception of two who had hypertension. The authors postulate that the consistent finding of decreased renal blood flow and glomerular filtration rate, regardless of whether or not there is impairment of the ability of the tubular cells to excrete para-amino hippuric acid, is suggestive of a reduction in the effective vascular bed in the kidneys rather than of the level of blood pressure or degree of hydration of the patients. The authors also suggest that the failure of any of the functions to improve with medication may have been due to insufficient dose of adrenal cortex extract, insufficient time of study, and irreversible structural or functional changes in the kidneys. Finally, the factors responsible for maintenance of function mentioned may not have been present in any of the preparations used. The

failure of testosterone propionate to restore maximum excretory capacity in females was felt to be due to the absence from testosterone of the hormonal factors which maintain this function, factors however, that may undoubtedly be supplied by the male testis —*T.H. McG.*

GONADS

BALZE, FELIPE A. DE LA: The progesterone withdrawal test or "medical curettage." Diagnosis and classification of amenorrheas, *Semana méd.* **55:** 953–963, 1948.

The test, originally introduced by Albright, makes use of intramuscular injections of 5 mg. of progesterone daily for five days. Menstruation occurring within five days indicates an adequate estrogen production and mildly subnormal ovarian activity whereas failure to menstruate proves severe ovarian failure. The test was applied to 56 women and compared with the results of vaginal cytological examinations and determinations of gonadotropic hormones in the urine. The test is recommended for its simplicity, reliability and rapidity.—*A.E.M.*

BENDER, S.: The value of the Guterman test in threatened abortion, *J. Obst. & Gynaec. Brit. Emp.* **54:** 783–792, 1947.

A series of 57 cases clinically characterized as threatened abortion were studied by the Guterman test. This was found to be a rapid, effective, and economical way of distinguishing cases of threatened abortion due to progesterone deficiency, as shown by the urinary pregnanediol excretion. The majority of threatened abortion cases did not show progesterone deficiency; only 11 out of 39 cases showed a negative Guterman test. In 28 patients having a positive Guterman test, the administration of progesterone seemed to have no significant effect in forestalling abortion in the six patients so treated. A possible cause for the threat to pregnancy was found in only six. In a group of 11 showing a negative Guterman test only one of five given progesterone aborted, whereas of the six not so treated only one failed to abort. The authors feel that progesterone given in the absence of progesterone deficiency may favor abortion. They recommend the simultaneous use of the Guterman test and a rapid pregnancy test to help differentiate other conditions from threatened abortion.—*R.A.C.*

FARRIS, E. J.: The prediction of the day of human ovulation by the rat test as confirmed by fifty conceptions, *Am. J. Obst. & Gynec.* **56:** 347–352, 1948.

The author studied the time of ovulation in 46 women as determined by reaction of the immature rat's ovary to the hypodermic injection of the urine of the patient. A positive response is hyperemia of the rat's ovaries. Two hundred and eight ovulations were so studied. The lengths of the cycles varied from 24 to 35 days. Conception occurred from cycle day 8 through 19. Sixty per cent of the women conceived on cycle days 11 to 13. The interval between ovulation and the onset of menstruation in the control cycles, during which there was no exposure to pregnancy, ranged from 12 to 20 days, averaging 14.8 days.—*C.D.D.*

HALBRECHT, J.: Further observations on the basal temperature in sterile women, *J. Obst. & Gynec. Brit. Emp.* **54:** 848–852, 1947.

From temperatures taken orally or rectally before arising in the morning basal tem-

perature curves were constructed covering over 1100 cycles of normally menstruating sterile women. These curves allow a diagnosis of early pregnancy, delayed menstruation, and early abortion. Desiccated thyroid, progesterone and estrogens do not change the temperature level. The normal rise in the second half of the cycle after ovulation is probably a complex mechanism, the corpus luteum being only one contributory factor. Endometrial biopsies were done in 90 cycles and gave identical results with basal temperature curves in 87 cases. Less than three per cent of all curves were unusable, which is less than the number of biopsies in which definite interpretation is impossible.—*R.A.C.*

KNIGHT, W. R.: Theca-cell tumors of the ovary with a report of 15 cases and a review of the literature, *Am. J. Obst. & Gynec.* **56**: 311–324, 1948.

One of the author's patients was studied for the presence of estrone and progesterone in the tumor tissue. The vaginal epithelium showed less than 2+ estrogenic activity as graded by the Shorr method. The biologic assay of the tumor showed 0.2 gamma of estrone in a 100 gram equivalent of the extracted tissue. Pregnandiol assay of a 24-hour urine specimen was negative. The author considers that the estrogen produced by thecoma, although small, may in the absence of progesterone account for the symptoms and frequent occurrence of associated pathology such as menstrual irregularities, post-menopausal bleeding, endometrial hyperplasia, adenomyosis, hypertrophy of the myometrium with uterine enlargement, uterine myoma, and endometrial carcinoma.—*C.D.D.*

KULLANDER, S.: Investigations into the determination of pregnanediol according to the Guterman method, *J. Obst. & Gynaec. Brit. Emp.* **55**: 159–170, 1948.

A manifestation of Guterman's qualitative method of determining pregnanediol is described. It allows a quantitative determination to be made. Neither the original nor the modified technique permit an accurate diagnosis of pregnancy. Large variations in individual excretion were found during the menstrual cycle and pregnancy. The author says the Guterman test is unreliable in the prognosis of threatened abortion.—*R.A.C.*

LOESER, A. A.: The action of intravenously injected sex hormones and other substances on the blood flow in the human endometrium, *J. Obst. & Gynec. Brit. Emp.* **55**: 17–22, 1948.

Using a specially constructed instrument consisting of thermocouples attached to a rubber catheter, changes in blood flow of the endometrium of the human uterus were measured. All hormones tested were injected intravenously, the sex hormones in propylene glycol. Natural estrogens, and to a lesser extent progesterone, produced a vasodilator action. Stilbestrol had only a slight but similar action. Testosterone produced constriction. Adrenalin and pituitrin had strong and lasting constrictor action.—*R.A.C.*

MORISON, C. R.: An investigation of the causes of sterility and lowered fertility in West African Negroes, *J. Obst. & Gynec. Brit. Emp.* **54**: 793–816, 1947.

Genital sepsis, chiefly gonorrhoea was the chief cause in 203 cases of sterility studied. Doubt is thrown on the current belief that the menarche starts earlier in African women. Genital maldevelopment and immaturity were found to be more prevalent than in European women. Observations on anovulatory menstruation and endometriosis were made,

though for comparative statistical purposes it is admitted the series is too small. Abortions were found to occur as frequently as in white races whereas uterine myomata, said to be more common in United States Negroes, were not more common in the African group than in whites. There was a virtual absence of psychological factors as a basis for sterility. Reasons are given for this difference.—*R.A.C.*

SEARLE, W. N.; HAINES, M., and BAKER, J. K.: Virilizing tumours of the ovary, *J. Obst. & Gynaec. Brit. Emp.* **55**: 135–141, 1948.

A 33-year-old primigravida developed hirsutism, hoarseness of the voice and hypertrophy of the clitoris about the 24th week of pregnancy. Psychologically she seemed normal except for irritability, which she attributed to consciousness of the startling change in her appearance. At the 27th week her blood pressure was found to be 170/120. She was delivered at full term of a normal 5 lb. 6 oz. male child, but failed to lactate. Otherwise the puerperium was normal. A month after confinement a laparotomy was done and an orange-sized cyst on a pedicle was found near the right broad ligament. This did not appear to be an arrhenoblastoma but is adequately described. Improvement in the hirsutism began three months after operation. A few ketosteroid values are recorded. Five years later the patient's appearance and blood pressure were normal.—*R.A.C.*

STALLWORTHY, J.: Facts and fantasy in the study of female infertility, *J. Obst. & Gynaec. Brit. Emp.* **55**: 171–180, 1948.

This article reviews the problem of infertility and cites the author's experience. He concludes that the most common cause of unilateral uterotubal blockage is poor coordination of tubal contraction and that uterine irritability is a potent factor in infertility. This may be due to psychological disturbances mediated by the autonomic nervous system as well as to hormonal influences.—*R.A.C.*

TWOMBLY, G. H.; MCCLINTOCK, L., and ENGELMAN, M.: Tissue localization and excretion routes of radioactive dibromestrone, *Am. J. Obst. & Gynec.* **56**: 260–288, 1948.

Equilin was brominated with radioactive bromine-82 to produce dibromestrone. This was injected into 12 rabbits, a monkey and 2 dogs. It was found that dibromestrone was not selectively localized in the rabbit in the adrenals, spleen, uterus, ovaries or testes. A high concentration occurred in the gall bladder within 6 hours of injection. Dibromestrone was not selectively localized in the liver, ovaries, or uterus of the monkey or the uterus of the dog. Dibromestrone was weakly estrogenic, if at all. Study was made of the gastro-intestinal tract of rabbits 30 minutes, 2 and 6 hours after intravenous injection. At two hours, 21.5 per cent of the injected dibromestrone was in the small bowel, 4.5 per cent in the cecum, and 0.8 per cent in the large intestine. By six hours, 1.8 per cent was in the small intestine, 12 per cent in the cecum and 10.9 per cent in the large intestine. Solubility tests were consistent with the hypothesis that dibromestrone was excreted into the bile and urine, largely as a phenolic steroid.—*C.D.D.*